Vol. 10 - No. 1 March, 1951

ANNALS OF THE RHEUMATIC DISEASES

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CONTENTS

	PAGE
Practical Considerations of the Use of Cortisone and ACTH in Rheumatoid Arthritis. R. H. Freyberg, M. Pattengale, H. Arnow, J. Dubrow, and C. H. Traub	1
Median Nerve and Synovial Changes in Lesions of the Carpal Tunnel. Edward W. Boland	10
Nylon Arthroplasty in Rheumatoid and Osteo-Arthritis. Alec G. Wilson and Theodore A. Potter	22
Progressions in the Treatment of Rheumatoid Arthritis. G. Newell Myers	32
Plasma and Serum Proteins in Certain Rheumatic Diseases. David B. Bier	46
Pregnancy in Ankylosing Spondylitis. P. Dornier Hall, A. C. H. Bird, and G. S. W. Organ	54
Spondylitis following Weil's Disease. H. Jones	61
Thermal Response in Rheumatoid Arthritis. A. Woodbridge	65
Heberden Society	74
Empire Rheumatism Council	82
Ligue Européenne Contre le Rhumatisme	83
Società Italiana di Reumatologia	83
Royal College of Physicians, Chronic Rheumatic Diseases Committee	84
International Congress of Physical Medicine, 1951	84
Book Reviews	85
Correspondence	86
Abstracts	87-104

LONDON
BRITISH MEDICAL ASSOCIATION
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PRACTICAL CONSIDERATIONS OF THE USE OF CORTISONE AND ACTH IN RHEUMATOID ARTHRITIS*†

BY

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The original and subsequent reports concerning the clinical effects of cortisone and ACTH (Hench and others, 1949; Thorn and others, 1949; Freyberg, 1950; Thorn and others, 1950a, b, and c; Sprague and others, 1950; Hench and others, 1950) clearly indicate that these hormones have profound effects in the human, producing great benefit on various rheumatic states so long as the hormone is administered, and that these effects cease soon after the administration of the hormones is discontinued. In acute illnesses, such as attacks of gouty arthritis or acute rheumatic fever, administration of these hormones can be expected to benefit the patient greatly, and on account of the short periods of administration there is little or no difficulty from undesired physiological effects of the hormone-producing complications. In chronic illnesses, such as rheumatoid arthritis, greater difficulties surround the use of cortisone and ACTH, for it is evident that the underlying disease process is not eliminated by a short period of administration, and prolonged vigorous use may produce serious side-effects. The practical problem, therefore, is:

> How can cortisone or ACTH be *effectively* and *safely* used in patients with chronic rheumatoid arthritis ?

Three possibilities exist:

(1) Administering cortisone or ACTH in short courses separated by periods of rest;
(2) Sustaining the benefits of these hormones by other forms of treatment so that cortisone or ACTH should not need to be repeated for a long period;
(3) Developing an effective method for prolonged use without harmful results.

These different methods of management were tested and compared in 31 patients

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* Read at the Annual Meeting of the American Rheumatism Association, San Francisco, California, June, 1950. This paper was discussed jointly with three others at the meeting, and the complete discussion has already been reported in this Journal, 1950, 9, 394.

† These investigations were supported by the Fund for Research in Rheumatic Diseases, Hospital for Special Surgery; a grant from the Masonic Foundation for Medical Research and Human Welfare; and (in part) by a research grant from the National Institutes of Health, Public Health Service.

with rheumatoid arthritis who received cortisone, and in 22 patients who received ACTH, during the year ending May 31, 1950. The results are summarized below.

Interval Therapy.—Using one of the hormones for a short period with rest periods intervening—so-called "course treatment" or "interval therapy"—it was hoped that undesirable side-effects would be eliminated because of interrupted treatment, that the adrenals and/or the pituitary glands might not suffer important functional or structural changes, and that with successive courses of treatment, a step-wise lasting improvement in the arthritis might be attained. In seventeen patient-experiences with interval treatment using cortisone, and in fourteen patient-experiences with courses of ACTH, there was always significant improvement during the time the hormone was used, but in *all* patients relapse ensued after the hormone was stopped. No patient became increasingly better or relapsed less after successive courses.

Examples.

(*i*) ACTH was administered to a child aged 6, with arthritis Stage I (Steinbrocker and others, 1949); the disease quickly improved to a great degree and the erythrocyte sedimentation rate became normal. After the drug was stopped there was a prompt relapse. Reinstitution of the hormone again effected prompt improvement, but after the second course relapse again occurred, and the same thing happened a third time (Fig. 1).

(*ii*) A similar experience in an adult who received cortisone is illustrated in Fig. 2.

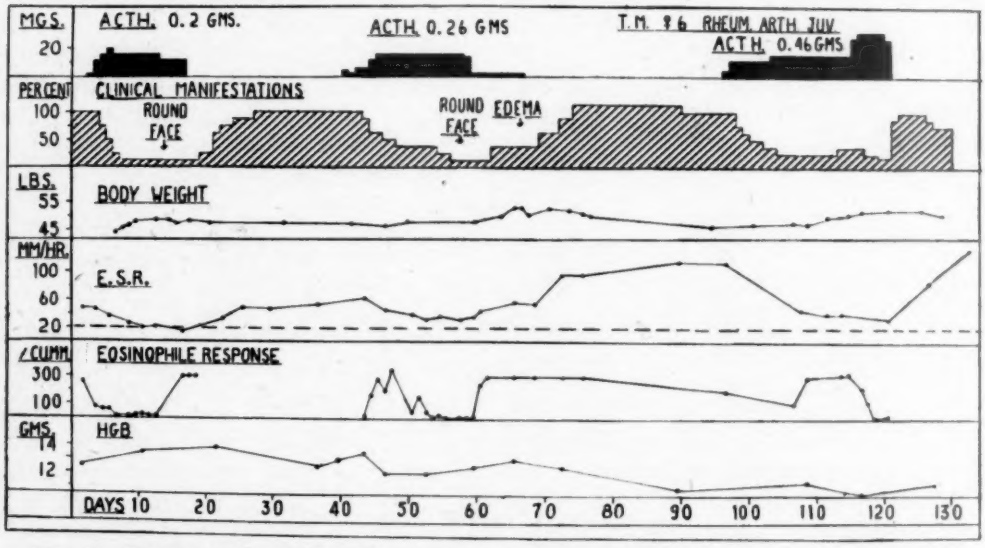

FIG. 1.—Response of a child with rheumatoid arthritis treated with "courses" of ACTH.

In all cases, short courses of hormone were well tolerated, but proved unsatisfactory since the speed and degree of relapse were unaltered after successive courses.

Efforts to Sustain Remission by Use of other Drugs.—It was hoped that after remission had been obtained by use of cortisone or ACTH, a less potent

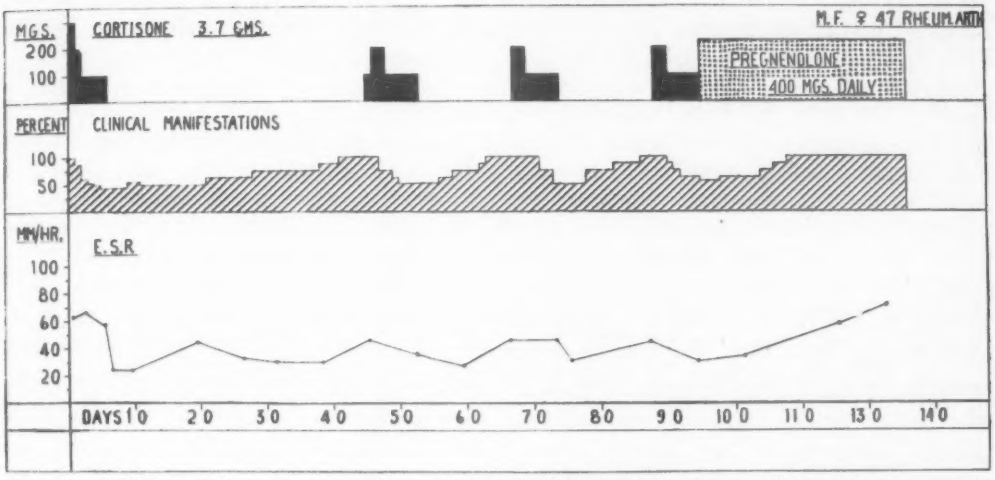

FIG. 2.—Effects of short " courses " of treatment with cortisone in an adult with rheumatoid arthritis.

anti-rheumatic drug might sustain the improvement. Several different medicines were tested for their ability to sustain remissions.

Gold.—In three patients treated with ACTH, and one treated with cortisone, gold thioglucose was injected in the customary manner *after* the hormone had been stopped. In one instance, benefits from the hormone (ACTH) continued for 4 weeks, then relapse began and progressed so that the pre-hormone condition was attained at the end of 8 weeks. In the other three cases, relapse began promptly after stopping the hormone and was soon complete. Used in this way gold therapy was of little or no value in preventing post-hormone relapse. Because of the slow effect of gold salts, they may be of greater benefit if begun many weeks before stopping hormone. This is now being tested.

Pregnenolone.—Results of the use of pregnenolone alone in 65 cases of rheumatoid arthritis in this clinic have been very poor. If pregnenolone had only weak anti-rheumatic effect, it might sustain the remission effected by cortisone or ACTH, but its use in this way failed completely in nine out of eleven cases in one group (Figs 2, 6, and 10). One patient retained most of the ACTH effect for 6 weeks while receiving pregnenolone orally in doses of 400 mg. daily, but then slowly relapsed.

Other Agents.—Pregnene triolone, testosterone, desoxycorticosterone acetate and ascorbic acid, and adenosine triphosphate all failed to sustain cortisone improvement (Table I).

TABLE I
EFFECT OF VARIOUS DRUGS USED TO SUSTAIN THE EFFECTS OF CORTISONE AND ACTH

Drug	Cortisone			ACTH		
	Good	Fair	None	Good	Fair	None
Pregnenolone	0	0	7	1	1	2
Pregnene Triolone ..	0	0	0	0	0	3
Gold Salts	0	0	1	0	1*	2
Testosterone	0	0	0	0	0	1
DOCA and Ascorbic Acid	0	0	1	0	0	0
Adenosine Triphosphate	0	0	0	0	0	1

* Sustaining effect temporary ; relapse after 1 month.

Prolonged Use of Hormone in Small Doses.—In July, 1949, studies were begun to determine three points with respect to the effects of cortisone and ACTH in patients with rheumatoid arthritis:

(1) The value of these hormones in doses less than the amount required to effect complete remission;
(2) The minimal effective dose required to sustain the desired result;
(3) The degree of safety of long-continued use of these hormones in maintenance therapy.

Three patients received ACTH, six had cortisone for more than 90 days without interruption, and three had cortisone for more than 200 days (209, 230, and 233 respectively). It is emphasized that the plan was to effect the desired (*not the maximal*) degree of remission, and then to attempt to sustain the benefits with smaller amounts or less frequent injections. Examples of our results are given graphically in Figs 3 to 8.

Examples.

(*i*) J.M., male, aged 40, with rheumatoid spondylitis was given only 400 mg. cortisone in 3 days; then injections of 100 mg. were made on only four, and later on only three days of each week, i.e. Monday, Wednesday, and Friday (Fig. 3). On this schedule improvement occurred so that only 40 to 50 per cent. of the clinical manifestations of disease remained. The erythrocyte sedimentation rate was reduced and the haemoglobin and weight increased. Complete remission did *not* occur, but improvement was considered very satisfactory by the patient. He did comfortably nearly everything he desired to do, including strenuous sports. This clinical condition

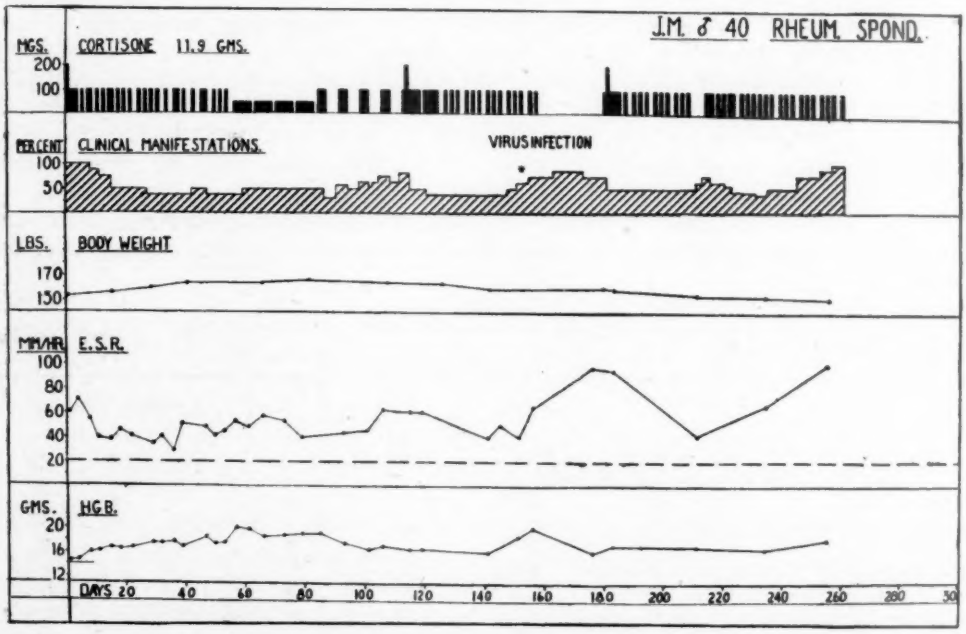

FIG. 3.—Effects of long-continued use of cortisone in an adult with rheumatoid spondylitis, showing comparative results of different dosage schedules.

remained quite constant for 40 days, then cortisone was injected in 50-mg. doses on six days of each week for a month. There was little change, although he did not feel or function quite as well, and the erythrocyte sedimentation rate increased slightly. Then, for the next month, the same amount of cortisone was given, but it was injected in doses of 100 mg. on only the first three days of each week. His condition deteriorated more during the four days when he did not receive the hormone, than it improved when he did receive it. After a course of " booster " treatment (daily injections), the arthritis again improved to its previous state where it remained for 5 weeks, when he contracted an infection and the hormone was discontinued. After the infection subsided, cortisone was resumed, and after 700 mg. had been injected in six consecutive days, 100 mg. were injected each Monday, Wednesday, and Friday, and again good improvement was maintained for about 2 months. Then, while continuing on this same regime, he gradually relapsed completely. For this patient, the best sustaining treatment was 100 mg. cortisone injected on Monday, Wednesday, and Friday. After a long period this proved to be insufficient, and " booster " treatment was planned.

(*ii*) W.H., male, aged 41, with rheumatoid arthritis shows the same process even more clearly (Fig. 4). In this patient initial improvement was sustained by 100 mg. cortisone three times a week for a period of 5 weeks, after which, although the same treatment schedule was continued, he gradually grew worse. " Booster treatment ", daily injections of 100 mg. cortisone for 15 days, re-established the same improvement, which was again sustained for 6 weeks by 100 mg. cortisone injected three times each week before relapse occurred. He again received the same type of booster treatment (fifteen daily injections) which produced the same degree of improvement which has continued satisfactorily for 12 weeks.

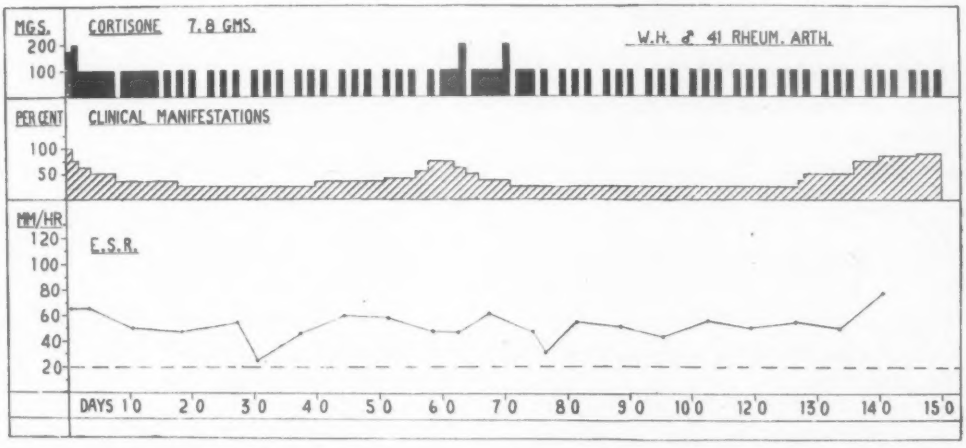

FIG. 4.—Effects of "maintenance treatment" with cortisone, and benefit from "booster" treatments, in an adult with rheumatoid arthritis.

(*iii*) D.D., male, aged 58, with moderately severe arthritis (Stage III) received 12·2 g. cortisone in two periods totalling 233 days (Fig. 5). A very good but not complete remission was accomplished by 1,750 mg. of the hormone injected during the first 13 days. This level of health, which satisfied both the patient and the physician, was nicely sustained by 100 mg. cortisone injected each second day for 105 days. As the hormone was gradually withdrawn over a 30-day period, he grew slowly but steadily worse. Without cortisone he lost all benefits, but he promptly improved greatly after the hormone was reinstituted; the improvement was again sustained by 100 mg.

on alternate days, later three times weekly, until after 60 days the hormone was gradually withdrawn. For more than 90 days he has maintained this improvement.

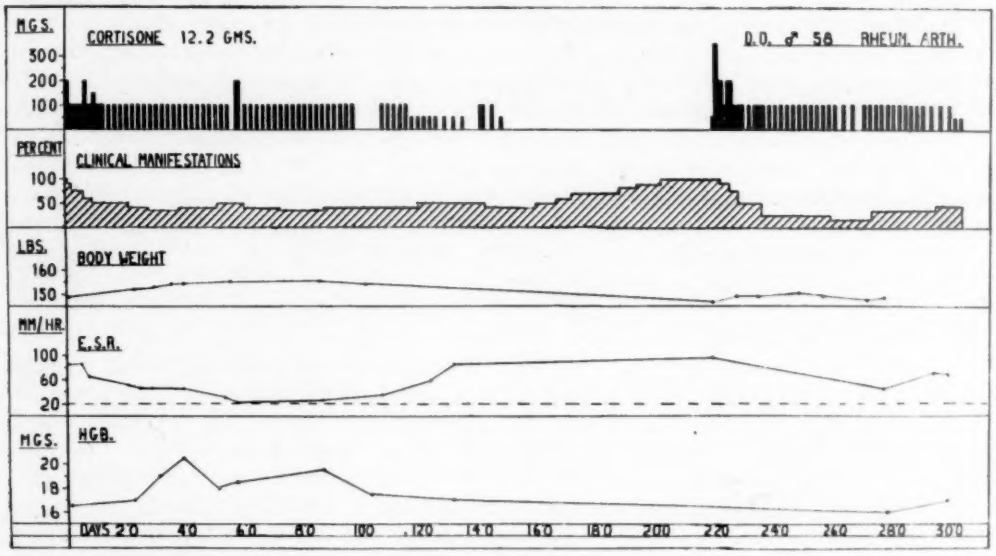

FIG. 5.—Effects of prolonged use of cortisone in an adult with rheumatoid arthritis.

(*iv*) M.S., female, aged 46, attained almost complete remission of arthritis (Stage II), by initial daily injections of cortisone; this improvement was sustained for 46 days by using 100 mg. cortisone three times a week. Injections of 100 mg. spaced at 5- to 7-day intervals were inadequate, she relapsed slowly but completely. Pregnenolone failed to maintain the benefits of a short booster treatment (Fig. 6).

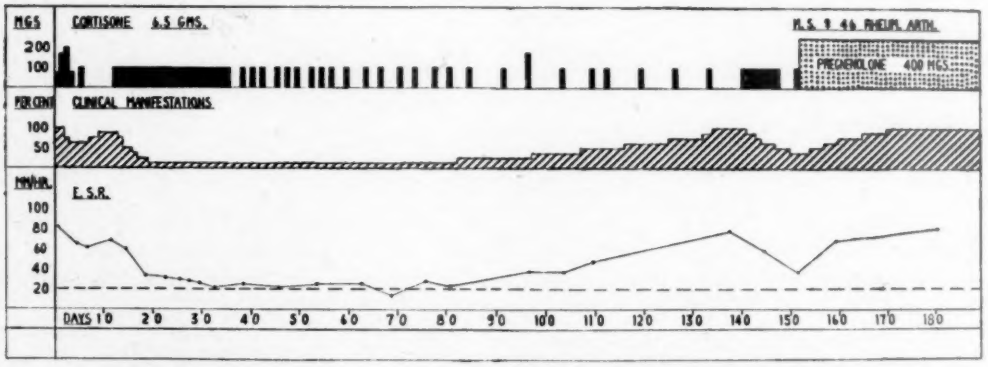

FIG. 6.—Excellent remission during "maintenance therapy" with cortisone, and failure of pregnenolone to sustain remission, in an adult with rheumatoid arthritis.

These examples illustrate that in many cases injections of cortisone given every second day, or three times weekly, may maintain a good remission of rheumatoid arthritis for many weeks. Three long-term cases to whom ACTH was administered

required injections two or three times a day to maintain benefit. With ACTH, we had no cases of drug-fastness.

This type of long-term treatment with cortisone generally gave good results. It was also gratifying that in all instances side-effects were not encountered or were of only a minor nature. In four cases treated with cortisone as described for long periods (the longest 233 days) there were *no* side-reactions (Table II). Electrolyte changes, oedema, abnormalities of carbohydrate metabolism, and vasomotor effects could be readily prevented or corrected; the few side-effects encountered were all reversible, and no important nervous-system changes occurred.

TABLE II
SIDE-REACTIONS ENCOUNTERED DURING PROLONGED USE OF CORTISONE AND ACTH

Patient	Sex	Age	Treatment			Nature of Reaction
			Duration (days)	Drug	Dosage (g.)	
G.F.	M.	60	91	ACTH	1·8	Oedema, mild; Tachycardia, mild.
F.S.	F.	28	104	ACTH	3·7	Acne, moderate; Rounding of face; Hirsutism; Oedema, mild.
R.E.	M.	56	112	ACTH	4·1	Rounding of face, mild.
M.S. (Fig. 6)	F.	46	149	Cortisone	5·8	None.
N.M.	F.	59	150	Cortisone	7·6	Oedema, moderate.
W.H. (Fig. 4)	M.	41	124	Cortisone	8·7	None.
J.M. (Fig. 3)	M.	40	260	Cortisone	11·9	None.
O.S. (Fig. 7)	M.	34	317	Cortisone ACTH	11·9 0·7	None.
D.D. (Fig. 5)	M.	58	150	Cortisone	7·2	Tachycardia, mild.
			90	Cortisone	5·0	Tachycardia, mild.

We were particularly anxious to ascertain whether prolonged administration of cortisone might cause or allow suppression of function of the patient's adrenal glands. There was some suggestion of this in one of our cases (O.S.) to whom, after the use of cortisone for 70 days, ACTH was administered in doses of 60 to 90 mg. daily for several days, during which time there was a distinct deterioration and no apparent good effect of the ACTH (Fig. 7, p. 8). Two days and four days after cortisone had been stopped, there was no lowering of blood eosinophils after the injection of ACTH. For 30 days after cortisone was discontinued there was poor eosinophil response after ACTH stimulation, although the trend was towards improvement (Table III, p. 9). In other patients ACTH eosinophil tests showed poor adrenal response during cortisone treatment.

In one patient (M.S., example (*iv*) above) no eosinophil decrease occurred when tested on the 46th day of cortisone (showing no adrenal stimulation), but on the 100th day *after* cortisone was discontinued, there was an excellent (normal) response indicating recuperation of this adrenal function which had been lowered during the use of cortisone.

In another patient (D.D., example (*iii*) above) several tests of eosinophil responses following ACTH injection *during* prolonged cortisone therapy, showed no significant

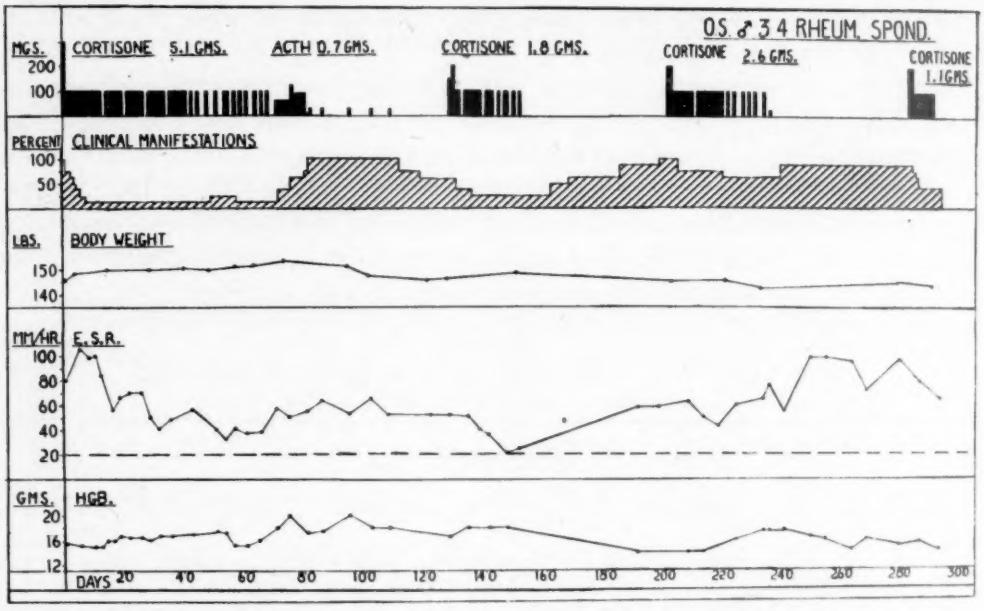

FIG. 7.—Effects of repeated use of cortisone in an adult with rheumatoid spondylitis. Note ineffectiveness of ACTH used directly after cortisone.

change, but there was progressive improvement in the eosinophil response after the hormone was discontinued, so that on the 35th and again on the 84th day after treatment there was a normal (50 per cent.) decrease, suggesting recovery of the adrenal function measured by this test 5 to 8 weeks after the prolonged use of cortisone. At no time was there any clinical indication of hypo-adrenalism. This important problem of the effect on the adrenals of the prolonged use of cortisone is being studied further.

Treatment of Children

At the beginning of these studies we had had little experience in the treatment of children, so that the dose required was not known. To determine if the cortisone requirement in children is related to body size, a dosage formula based on the ratio of surface area was tested. Each child was given a dose corresponding to the average adult dose (100 mg. daily) in the same ratio as its body weight corresponded to 150 lb. In all five children the results were similar.

Examples.

(*i*) P.S., female, aged 13, with arthritis (Stage IV), improved slightly and quite slowly on the formula dose (67 mg. daily) compared with the usual response in adults. When the dose was doubled or tripled there was increased improvement, but side-effects were also seen, notably round face, acne, and oedema. Later the inadequacy of 50 mg. of cortisone daily was striking; improvement followed 100 mg. daily, but even then was less than observed in many adults receiving this dose (Fig. 8, p. 10).

(*ii*) In one child with *early*, *mild* arthritis (Stage I), 16 to 20 mg. ACTH daily proved quite effective.

TABLE III
EOSINOPHIL RESPONSE DURING AND AFTER ACTH STIMULATION IN PATIENTS WHO HAD RECEIVED LONG COURSES OF CORTISONE

Patient	Sex	Age	Cortisone Administration (days)	Total Amount (mg.)	Days after Discontinuation of Cortisone	Eosinophil Reduction 4 hrs. after 25 mg. ACTH (per cent.)
O.S. (Fig. 7)	M.	34	68	5,100	2	—11
					4	—13
					7	28
					9	39
					11	29
					13	47
					22	30
					28	51 (75 mg. ACTH)
J.M. (Fig. 3)	M.	40	75	3,800	During	18
			77	3,900	,,	45
			88	4,500	,,	26 (50 mg. ACTH)
			Second period 5	600	,,	33
			6	700	,,	22
			35	1,800	,,	34
W.H. (Fig. 4)	M.	41	65	4,675	During	25
			104	6,575	,,	8
			128	7,575	,,	14
D.D. (Fig. 5)	M.	58	Second period 74	4,000	During	—15
			87	4,600	,,	10
			93	4,800	4	—19
					14	6
					35	59
					84	50
M.S. (Fig. 6)	F.	46	148	5,600	During	—15
				6,400	100	77

These data indicate that a child's hormone requirement is not proportional to body size, but more likely depends upon the severity of the arthritis, and may approximate to or equal the average adult requirement. In children side effects were more frequent and may be more troublesome than those encountered in adults.

Oral Administration

An important practical difficulty in the use of cortisone and ACTH in a chronic illness such as rheumatoid arthritis, is that the presently available preparations of these hormones require intramuscular injections. This makes most patients dependent upon another person for his medicine. If one of these hormones were effective orally, its clinical use would be greatly facilitated. The protein nature of ACTH makes it unlikely that it would be effective if taken into the intestinal tract. Recently, through the courtesy of Dr. James Carlisle, of Merck and Co. Inc., we had a small supply of tablets, each containing 100 mg. cortisone. The effects of these tablets were studied in four patients with rheumatoid arthritis.

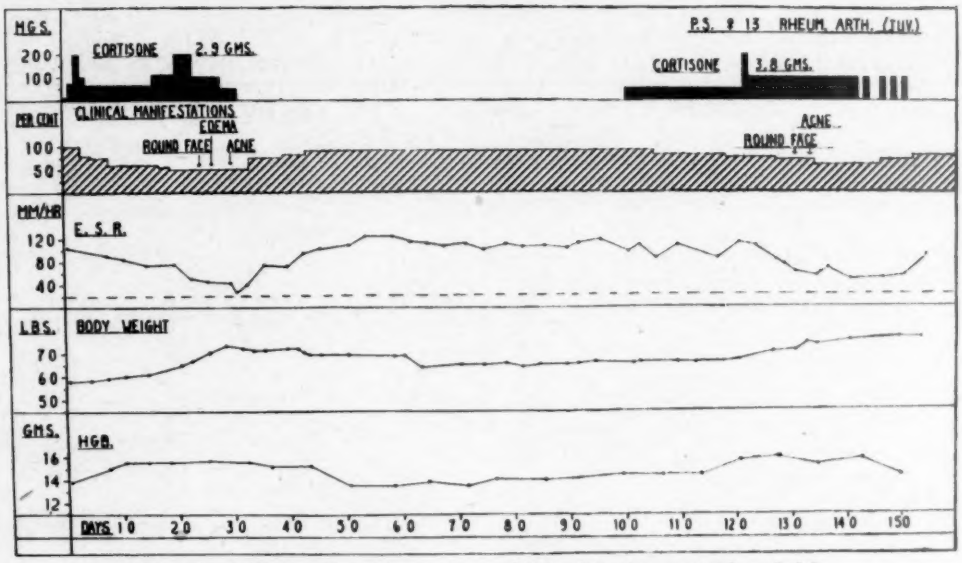

FIG. 8.—Effects of cortisone in a child with rheumatoid arthritis.

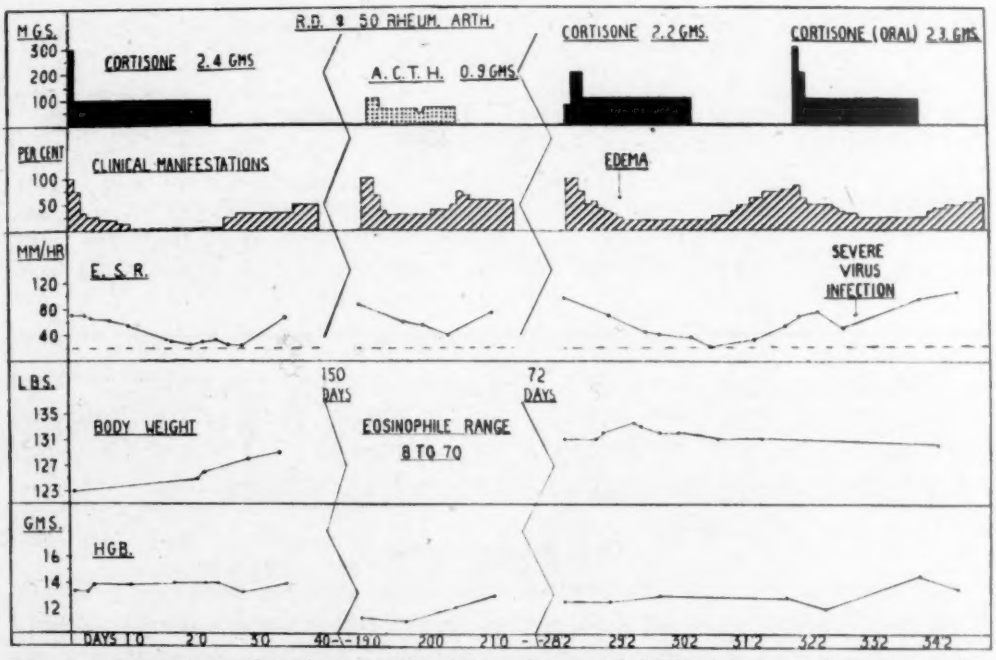

FIG. 9.—Comparison of cortisone orally with cortisone and ACTH intramuscularly in an adult with rheumatoid arthritis.

Examples.

(*i*) R.D., female, aged 50, rheumatoid arthritis (Fig. 9), enabled us to compare the previous results of intramuscular injections of cortisone acetate suspension (two periods), and ACTH (one period). Cortisone given orally for 20 days in doses similar to those used parenterally, had a slightly slower, but excellent anti-rheumatic effect, even during a severe virus infection which probably kept the sedimentation rate elevated.

(*ii*) E.F., female, aged 45, who had severe arthritis (Stage IV), received cortisone orally for 19 days (Fig. 10). On the first day, 300 mg. were given, on the second, 200 mg., and then 100 mg. daily. The initial anti-rheumatic effect was excellent but quickly lessened; after the daily oral dose was raised to 200 mg. there was again an excellent clinical improvement, with reduction of sedimentation rate, and increase in body weight and haemoglobin—results comparable to those usually effected by the

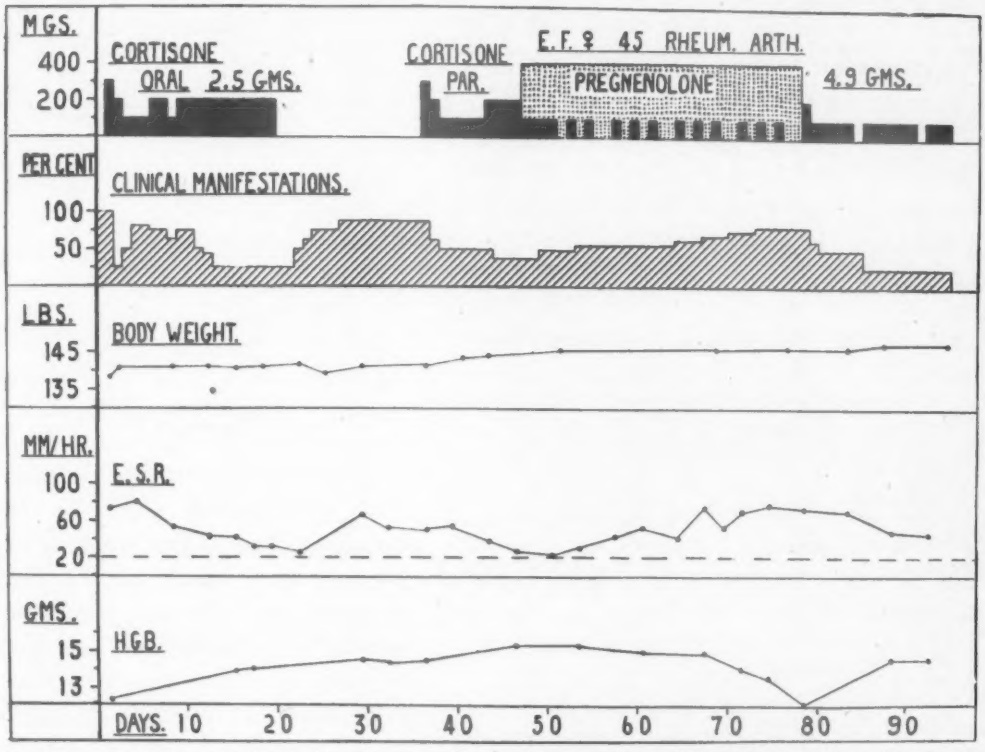

FIG. 10.—Initial good effects of cortisone orally, and comparison with subsequent use of cortisone intramuscularly and pregnenolone orally.

hormone when given intramuscularly. Relapse followed the cessation of oral therapy. With intramuscular injections of cortisone in amounts comparable to the oral doses, changes occurred similar to those produced by cortisone tablets. Benefits were not sustained by injection of 100 mg. three times weekly even though pregnenolone was used simultaneously.

Two other patients with severe arthritis (Stage IV) had good improvement from oral cortisone given for 9 days.

The effectiveness of oral cortisone has thus been demonstrated in four patients. Two patients who received the hormone by both routes, expressed preference for oral cortisone because the effect was considered to be smoother. Studies to determine the best method of oral use of cortisone are now in progress.

Intra-Articular Injections

After Hollander reported his studies of intra-articular injections of cortisone, we injected cortisone 42 times into the joints of eight patients. Amounts up to 50 mg. given intra-articularly have not irritated the joint capsule.

Example.

F.C., male, aged 50, suffered from rheumatoid arthritis. After one injection of 25 mg. cortisone into the joint, the amount of synovial fluid decreased and the total number of cells and leucocytes in the fluid of the injected joint were reduced in contrast to small changes in the fluid of the opposite untreated knee. With successive injections the fluid became too little to aspirate, inflammation, pain, and stiffness lessened, and joint function improved (Fig. 11).

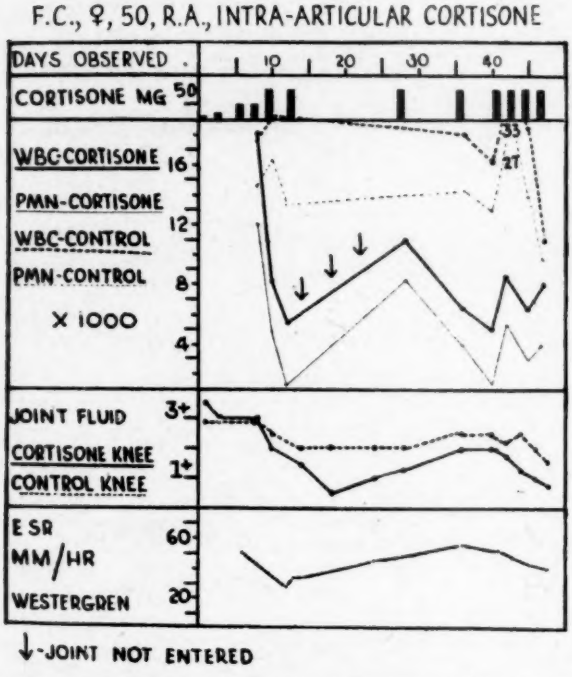

FIG. 11.—Changes effected by cortisone injected intra-articularly, compared with effects of sterile saline injected for control purposes into the companion joint. Arrows indicate attempts to enter the cortisone-injected joint which were unsuccessful because so little fluid was present within the capsule.

These data are further indications that cortisone exerts its effect at the connective tissue level. Such intra-articular injections have been of temporary practical value to several patients and might be expected to be useful in non-articular arthritis, or in instances when one joint is the only cause for disability.

Summary*

Investigations to date indicate that cortisone and ACTH do not cure any illness, but, like other hormones, have profound pharmacologic effects. Their use is more difficult in *chronic* illnesses, for their desired beneficial effects may be complicated by side-reactions, some of which may be detrimental to the patient's best welfare. In patients with rheumatoid arthritis our studies indicate that variations in effect largely depend upon the amount of the dose and the manner of administration.

Repeated short periods of treatment did not result in greater or more sustained improvement after successive treatments.

To sustain the improvement effected by cortisone or ACTH, pregnene triolone, adenosine triphosphate, testosterone, pregnenolone, and gold-salt therapy begun *after* withdrawal of the hormone, usually failed, or were poor and undependable.

The best method of sustaining the improvement initially obtained, was to continue the use of the hormone in smaller amounts or less frequently. In several

* Since this article was written much more has been learned regarding the effects of cortisone and ACTH in patients with rheumatoid arthritis, particularly concerning the benefits and tolerance of the hormones, the complications during administration, the changes following withdrawal. We do not intend to imply that prolonged administration of cortisone and ACTH is generally recommended for rheumatoid arthritis; the exact place of these hormones in practical therapy is still to be determined.

cases, cortisone injected three or four times weekly in doses of 100 mg., sustained good improvement.

With such maintenance therapy, the undesirable effects of the hormone were infrequent and mild even when its use was continued for 200 to 233 days. In more severe arthritis, " booster treatment " of daily injections for 5 to 14 days may be required at intervals of 4 or 5 weeks; in *very severe* disease, daily injections may be needed indefinitely.

The prolonged use of cortisone may suppress adrenal function; further studies are being conducted to determine the importance of this, and to ascertain the factors affecting the reversibility of this suppression. Our experience indicates that it is often better to maintain a good but *not maximal* anti-rheumatic effect with the least possible amount of hormone. Even after prolonged treatment, relapse tends to occur when the hormone is withdrawn. Gradual withdrawal usually affords a smoother post-hormone adjustment.

In children, hormone requirement is apparently not governed by body size, but by the severity of the disease. Doses approximating to the average adult requirement may be needed for good anti-rheumatic effect, but the problem of side-effects then is greater.

Cortisone was shown to be an effective anti-rheumatic agent when administered orally.

Local effects were demonstrated when cortisone was injected intra-articularly.

In order to be of *practical* use in rheumatoid arthritis these hormones must be able to be administered easily to ambulant patients. The frequent intramuscular injections required with the present preparations complicate their prolonged use, especially that of ACTH. The demonstration of the effectiveness of cortisone given orally, and into the joint should therefore be of importance. If cortisone is prepared for oral administration, abuse of this powerful hormone must be avoided.

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Considérations d'Ordre Pratique sur l'Emploi de la Cortisone et de l'ACTH dans l'Arthrite Rhumatismale

RÉSUMÉ

Des recherches jusqu'à l'heure actuelle indiquent que la cortisone ou l'ACTH ne guérissent aucune maladie mais, comme toute autre hormone, ont des effets pharmacologiques profonds. Leur emploi est plus difficile dans les maladies chroniques, car l'effet favorable qu'on recherche peut se compliquer par des réactions secondaires qui pourraient porter préjudice au bien-être

des malades. Nos études montrent que chez des malades atteints d'arthrite rhumatismale les variations de l'effet dépendent presque entièrement de la dose et du mode d'administration.

Des courtes périodes répétées de traitement ne suffisaient pas pour augmenter ou même pour stabiliser l'amélioration obtenue par le traitement initial.

Pour maintenir l'amélioration produite par la cortisone et l'ACTH, après avoir cessé leur administration, les substances suivantes furent essayées : pregnène triolone, triphosphate d'adénosine, testostérone, pregnénolone et sels d'or. Ces tentatives échouèrent ou bien aboutirent à des résultats minimes et incertains.

La meilleure méthode pour maintenir l'amélioration initiale consistait en l'emploi de l'hormone en quantité réduite ou bien aux doses plus espacées. Dans plusieurs cas l'amélioration pouvait être maintenue par des injections de 100 mg. de cortisone 3 à 4 fois par semaine.

Au cours de ce traitement de maintien des réactions secondaires à l'hormone furent rares et benignes, même quand on l'administrait pendant 200 à 300 jours. Dans des cas d'arthrite plus grave un traitement intensif d'injections quotidiennes pendant 5 à 14 jours peut être nécessaire toutes les 4 ou 5 semaines ; dans des cas très graves des injections quotidiennes s'imposent indéfiniment.

L'administration prolongée de la cortisone peut supprimer la fonction corticorénale. L'étude de ce problème continue, pour en déterminer la portée et pour trouver les facteurs qui affectent la reversibilité de ce phénomène. Nos expériences indiquent qu'il est souvent préférable maintenir un effet anti-rhumatismal bon, mais pas nécessairement le meilleur, avec la moindre quantité possible de hormone. Même après un traitement prolongé des rechutes tendent à se produire chaque fois que l'on arrête l'administration de l'hormone, mais la probabilité de la rechute diminue au fur et à mesure que le traitement se prolonge. La suppression progressive permet généralement une adaptation post-hormonale plus douce.

Chez les enfants le besoin d'hormone est apparemment déterminé non par leur taille mais par la gravité de la maladie. Pour obtenir un effet antirhumatique satisfaisant des doses approchant celles des adultes peuvent être nécessaires ; d'autre part le problème des réactions secondaires acquiert une importance plus grande.

Il a été démontré que la cortisone est efficace contre le rhumatisme quand on l'administre par la voie buccale.

On observa des réactions locales après l'administration intra-articulaire de la cortisone.

Du point de vue pratique, pour traiter l'arthrite rhumatismale, l'administration des hormones aux malades ambulants devrait être facile. La nécessité d'injections intramusculaires fréquentes des préparations employées à présent rend leur emploi onéreux, surtout en ce qui concerne l'ACTH. L'efficacité de la cortisone par la voie buccale et intra-articulaire est donc d'une grande importance. Il faudra prendre de grands soins pour éviter l'abus de la préparation orale de cette hormone puissante.

Consideraciones Prácticas Sobre el Empleo de la Cortisona y de la ACTH en la Artritis Reumatoide

Resumen

Las investigaciones hasta la fecha indican que la cortisona o la ACTH no curan enfermedad alguna sino, como otras hormonas, tienen hondos efectos farmacológicos. Su empleo es más difícil en las enfermedades crónicas, ya que el efecto favorable intentado puede complicarse con reacciones secundarias, con el perjuicio del enfermo. Nuestros estudios demuestran que en los artríticos reumatoides las variaciones del efecto dependen casi enteramente de la dosis y del modo de administración.

Períodos cortos y repetidos de tratamiento no bastan para aumentar y ni siquiera para estabilizar la mejoría obtenida con el tratamiento inicial.

Para mantener la mejoría producida por la cortisona y por la ACTH después de haber interrumpido la administración de éstas, fueron empleados : pregnene triolone, trifosfato de adenosina, testosterona, pregnenolona y sales de oro. Estas tentativas fracasaron o dieron resultados mínimos e inseguros.

El mejor método para mantener la mejoría inicial producida por la cortisona y la ACTH consistía en administrar la hormona a intervalos más largos o en cantidades reducidas. En muchos casos 3 o 4 inyecciones por semana de 100 mg. de cortisona bastaban para mantener la mejoría.

En el curso del tratamiento de sostén las reacciones secundarias a la hormona fueron raras y benignas, aun cuando la administración había durado 200 a 300 días. En casos de artritis grave se puede necesitar un tratamiento de choque de 5 a 14 inyecciones diarias consecutivas cada 4 o 5 semanas ; en casos muy graves inyecciones diarias habrán de continuarse indefinidamente.

La administración prolongada de la cortisona puede suprimir la función adrenal. Este problema está al estudio para determinar su importancia y para hallar los factores interesados en la reversibilidad del fenómeno. Según nuestra experiencia, a menudo más vale mantener un efecto anti-reumático bueno, pero no el mejor, con la menor posible cantidad de hormona. Aun después del tratamiento prolongado, al cesar la administración de la hormona, recaídas suelen producirse,

pero cuanto más dura el tratamiento tanto menos posible es la recaída. La privación gradual permite generalmente una adaptación post-hormonal más suave.

En los niños el requerimiento de hormona no parece estar determinado por el tamaño del cuerpo sino por la gravedad de la enfermedad. Para obtener un efecto anti-reumático satisfactorio se pueden necesitar dosis casi tan fuertes como las para adultos ; aquí la cuestión de las reacciones secundarias adquiere mayor importancia.

Se ha demostrado la eficacia antirreumática de la cortisona por la vía oral.

Después de la administración intra-articular de la cortisona fueron observadas reacciones locales.

Desde el punto de vista práctico, para tratar la artritis reumatoide es preciso que estas hormonas se puedan administrar facilmente a enfermos ambulantes. La necesidad de inyecciones intramusculares frecuentes de las preparaciones empleadas hasta ahora complica su empleo, particularmente cuando se trata de la ACTH. El hecho que la cortisona es eficaz por vía oral e intra-articular tiene, por consiguiente, gran importancia. Habrá que tener mucho cuidado con la preparación oral para evitar el abuso de esta hormona poderosa.

MUSCLE, NERVE, AND SYNOVIAL CHANGES IN LUPUS ERYTHEMATOSUS*

BY

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In disseminated lupus erythematosus synovial and muscle manifestations are prominent clinical features, but only meagre histopathological studies of these tissues have been made in this disease. We have undertaken, therefore, to investigate pathological changes in the striated muscle, peripheral nerves, and synovia of patients dying of lupus erythematosus.

Method

All material used was autopsy material. Lupus erythematosus was in all cases the primary cause of death. Muscle was available in fifteen cases, peripheral nerves in fifteen, and synovia in five. The tissue was embedded in paraffin blocks and serially sectioned. A minimum of 300 serial sections were cut from each block, and every tenth section was mounted and stained for study.

As controls, muscles and nerves were obtained from thirty other autopsies and prepared in a manner identical to the above. In addition, material from ten cases of rheumatoid arthritis was obtained and similarly studied. These latter findings are being more fully reported elsewhere.

Findings

The prominent changes which have been noted are muscle degeneration, and venous changes consisting of three phases: oedema, reaction, and sclerosis.

Muscle degeneration in the cases of lupus occurred much more frequently than in the control group. It was usually of slight to moderate extent and rarely generalized. It appeared focally or in a disseminated pattern. It was not possible to correlate focal muscle degeneration with focal vascular changes, although they were never completely dissociated. The degeneration varied from early loss of striations to old falling out of muscle tissue with fibrotic replacement. The changes varied from muscle to muscle in the same patient.

The vascular involvement in the muscle and nerve tissue from lupus cases was widespread and characteristic. It was typically venous in location with only occasional involvement of the arterial side of the system. It appeared that the initial phase was an acute oedematous phlebitis in which the vein wall was markedly thickened and hydropic in appearance and the cells of the wall swollen. This seemed to progress to a secondary reactive phase in which the vein wall underwent a reactive reparative process as evidenced by the presence of many cells both within

* Read at the Annual Meeting of the American Rheumatism Association, San Francisco, Calif. June, 1950.

and about the vessel wall. The early reactive lesion showed a central zone of large mononuclear cells having vesicular nuclei, and an outer zone of lymphocytes in a ratio of about 1 : 1. Fibroblasts were evident early, and occasional plasma cells and an infrequent eosinophil were seen peripherally. In the older reactive lesions the mononuclear cells were less numerous or absent, as were also fibroblasts, and there was then left a collar of lymphocytes within and about a condensed, thickened vein wall. In serial sections it was seen that this peri-vascular reaction was nodular in character, involving segments of the length of the vessel rather than its entire extent, the intervening uninvolved portions of the veins being of normal appearance. In the third or sclerotic phase, the cell aggregates were gone and there remained varying degrees of sclerotic thickening of the vein wall. It is not necessarily assumed that the reactive phase is essential for production of the sclerotic phase, particularly in view of the thesis of Klemperer and others (1941) that a variation in the tempo and intensity of injury may directly bring about sclerosis.

The vascular pattern of reaction noted in these lupus sections is identical with that found by us in some active cases of rheumatoid arthritis. It is similar to the reaction found in periarteritis nodosa, except that the latter predominantly involves the arterial side of the circulation with a venous overflow, the reverse of the involvement noted above. In this investigation of muscle and nerve changes, synovia from five cases of lupus were obtained and similarly studied by serial sections. In these synovia, the vascular changes were identical with those noted in the muscles and nerve sections, but in addition, the CT stroma was involved early with diffuse swelling. With progression of the vasculitis to the cellular reactive stage there was a stromal fibroblastic response and numerous young fibroblasts appeared. Ultimately, with subsidence of the process, the stroma returned to normal or residual sclerosis of vessels and fibrotic thickening of the CT stroma remained. The synovial-lining cells were little affected.

Muscle degeneration was noted in eleven (73 per cent.) of the fifteen lupus cases (Fig. 1), as contrasted with 37 per cent. of the thirty controls. The muscle degeneration in the

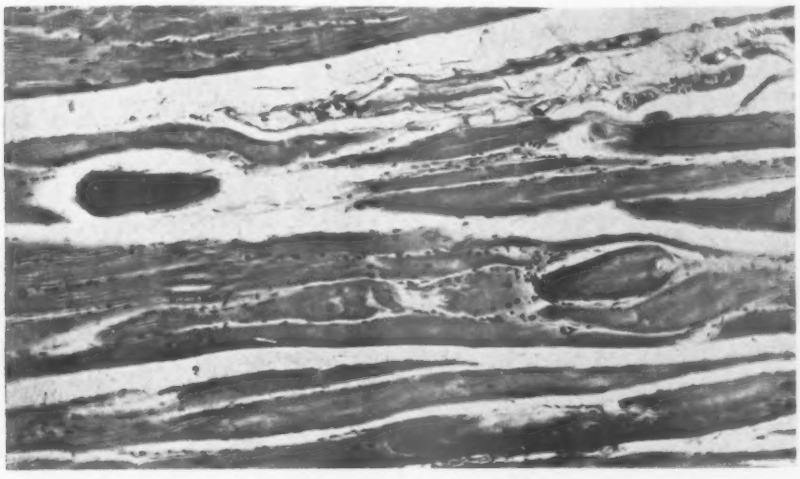

FIG. 1.—Focal muscle degeneration in lupus erythematosus. ×85.

control cases could usually be accounted for by the fatal disease processes. Clawson and others (1947) found from a study of 450 consecutive autopsy cases that atrophy of Grade 1 or more was present in one or more muscle in 42·4 per cent. of cases; our incidence of 37 per cent. in this control series is thus in keeping with his figures.

Perivascular cell aggregates were present in the muscle in every case of lupus and in only four (13 per cent.) of the control cases. In the nerves studied serially from the fifteen lupus cases, perivascular cell aggregates were present in fourteen (93 per cent.), only one case showing no aggregates in any nerve section. Of the thirty control cases, only three (10 per cent.) showed such aggregates.

Arterial changes were only occasionally seen in the lupus cases, and arteritis was never seen without co-existing phlebitis. In the control group arterial changes were present in 27 per cent. and could be accounted for by underlying disease processes.

Veins prominently showed the oedematous phase of phlebitis in the muscles of two lupus cases (Fig. 2), and in occasional nerve sections. The reactive phase with its associated perivascular aggregation of cells was prominent in muscle in every case of lupus and in nerve sections from 93 per cent. (Fig. 3). The sclerotic stage of phlebitis was apparent in muscle from 46 per cent. and in nerve tissue from 73 per cent. (Fig. 4, opposite).

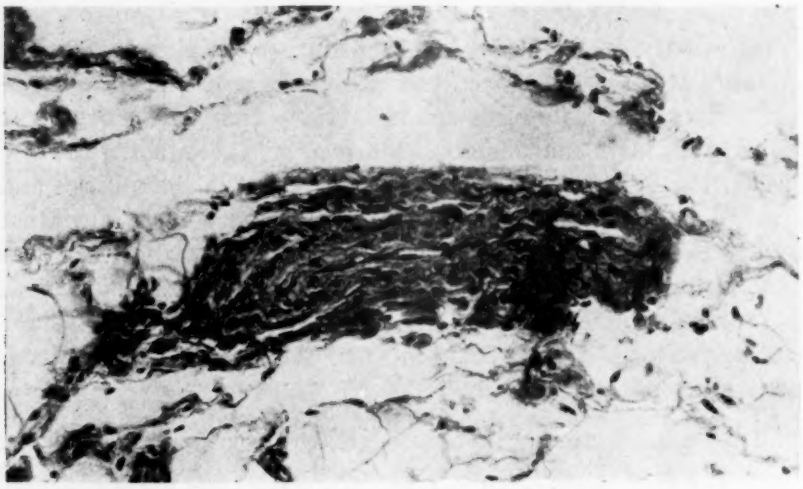

FIG. 2.—Oedema and thickening of a vein wall with the beginning of cellular reaction. ×235.

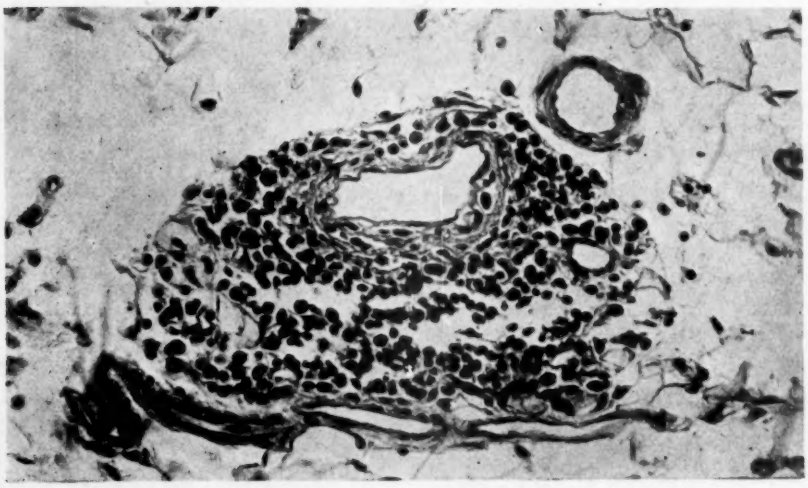

FIG. 3.—Venous and paravenous cellular reaction, reactive phase. ×235.

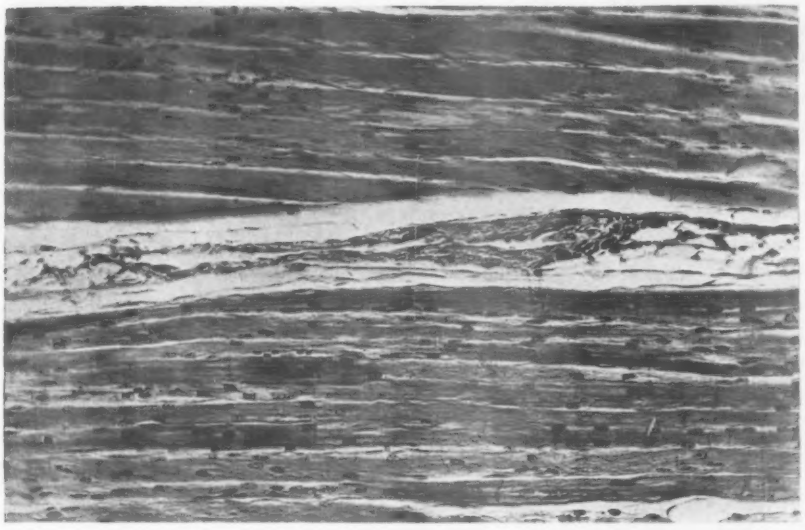

FIG. 4.—Sclerotic, or healed, stage of phlebitis. ×140.

In only one muscle section from one case of lupus was there material suggesting fibrinoid degeneration and no instances of endothelial proliferation were noted.

Definite nerve degeneration of slight to moderate degree was noted in 53 per cent. of the fifteen lupus cases and in 37 per cent. of the thirty control cases.

The volume incidence of perivascular cell aggregates in the reactive phase of phlebitis is of interest. An average of 4·1 muscles were studied in each case of lupus; of the total of 62 muscles from the fifteen cases, 35 (56·4 per cent.) showed perivascular cell aggregates. Of the 27 nerves from the fifteen cases of lupus, 21 showed similar aggregates. Among the thirty controls, only five of 240 muscle specimens (2·1 per cent.) and three of 110 nerve specimens (2·7 per cent.) showed positive findings.

Summary

(1) In serially sectioned muscles from fifteen cases of lupus, slight to moderate muscle degeneration was noted in 73 per cent.; 37 per cent. of thirty control cases showed similar changes.

(2) In lupus erythematosus a vascular pattern of reaction on the venous side of the circulation appears to consist of three phases: oedema, cellular reaction, and sclerosis. These muscle and perineural vascular changes of lupus are identical with those seen by us in some active cases of rheumatoid arthritis. Muscle and nerve degeneration and vascular change could not be correlated in degree and it cannot be decided whether the one is the cause or consequence of the other, or whether they are simultaneous concomitant responses to a common stimulus. Synovial tissue showed vascular changes identical with the pattern of reaction seen elsewhere. In addition, the stroma showed initial oedema and subsequent fibroblastic response with ultimate resolution or fibrosis. Synovial-lining cells showed only occasional hyperplastic changes.

(3) The identical nature of the vascular reaction in lupus with that noted in cases of active rheumatoid arthritis, and the similarity of the reaction to that seen in periarteritis nodosa is of speculative interest for further investigation.

(4) It could not be ascertained whether the reaction pattern is secondary to damage by an extraneous factor, or whether a hyperergic response is causing injury to the responding system.

Discussion

DR. JAMES W. KERNOHAN (*Rochester, Minn.*): I was much interested in the fact that the lesions are found in the veins rather than in the arteries. Regarding changes in lupus erythematosus and their relationship to other changes, Goeckerman (1923) pointed out that lupus erythematosus was not confined to the manifestation on the skin, but was also a systemic disease. Libman and Sacks (1924) showed valvular lesions in the heart, and Klemperer and others (1941) showed lesions in the kidneys. Now Dr. Lowman has shown changes in the muscles, nerves, vessels, and synovia; this also points to the fact that lupus erythematosus is a systemic disease affecting practically all the tissues in the body rather than one affecting only the skin.

I am still not sure why the changes occur in the muscles, whether they result from the degeneration of nerves or from action through the vascular system. I rather incline to the idea that they occur first in the vessels. It is true that Dr. Lowman was unable to find vascular changes in association with changes in the muscle in every case, but I still think the primary lesion is that in the walls of the blood vessels.

DR. J. J. BUNIM (*New York*): Dr. Lowman is to be congratulated for this very careful study in a rather difficult and controversial field. We were unable to find any changes on the venous side of the circulation in the skeletal muscle sections of patients with rheumatoid arthritis.* I noticed that Dr. Lowman was unable to find arterial changes in the muscles. Incidentally, I must emphasize that, like Dr. Lowman, we were dealing with changes in skeletal muscle, and not in the viscera.

I should like to ask whether Dr. Lowman considers the perivascular infiltration round the veins as diagnostic of lupus erythematosus. So often biopsies are carried out in the hope that the pathologist will support or rule out a clinical diagnosis of lupus erythematosus. I have not been able to get any pathologist, at least in New York, to commit himself to a diagnostic lesion in skin or muscle associated with lupus erythematosus. If the change Dr. Lowman reports is diagnostic, it would be extremely important, especially since it could be found in the skeletal muscle which could be subjected to biopsy.

We found no strict correlation between muscle and vascular changes.

DR. J. F. RINEHART (*San Francisco, Calif.*): It is an important and solid observation that these lesions have been found in nerves and muscles. However, it should be noted that such lesions are found all over the body. I am sure Dr. Lowman knows that they are widespread, but it should be made quite clear that this is so. As a matter of fact, I found them so widespread that last year, at the meeting in New York, I presented the idea that disseminated lupus is really a vascular disease. I have never been much impressed with "fibrinoid degeneration" as a specific lesion in the disease, and believe that most of it could be accounted for by widespread injury to small vessels, and that it represents to a large extent the escape of fibrin into tissues. Note that I say, *most* of it. There is some collagenous necrosis, but the vasculitis is a dominant feature of this disease. Even in the lesion seen in the spleen, with concentric perivascular collars of collagen, there is also evidence of injury to the intima and media of the splenic vessels.

DR. CHARLES RAGAN (*New York*): The histological changes found in these diseases depend upon the stage in the course of the disease at which the section is made.

I mention this because we have one patient who, in 1939, had what appeared clinically to be typical lupus erythematosus disseminatus, who was in fact very ill with pericarditis.

* A Paper entitled "A Vascular Lesion Observed in Rheumatoid Arthritis" was given by Drs. J. J. Bunim, L. Sokoloff, and S. L. Wilens at the Annual Meeting of the American Rheumatism Association, June, 1950. A summary of the paper and the ensuing discussion has already appeared in this Journal (*Annals of the Rheumatic Diseases*, 1950, 9, 388.)

By the time she died in 1948, there were no specific lesions of lupus present in a complete autopsy which was reviewed by Dr. Klemperer.

These lesions may be specific for lupus in the active phase, as Dr. Bunim has suggested, but I think we must keep in mind that this is a dynamic disease and that it depends upon the stage at which the lesions are removed whether they may be regarded as specific or not.

DR. LOWMAN: We did not wish to imply that this is by any means a diagnostic reaction. I am sure that it is a nonspecific reaction that occurs in many different conditions, and that it would be of no value in the diagnosis of lupus.

Secondly, we did not intend to imply that these changes occur solely in muscles or nerves; we investigated these particular tissues because of the clinical manifestations which we had seen, and because they had not previously been investigated.

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Modifications Musculaires, Nerveuses et Synoviales dans le Lupus Érythémateux

RÉSUMÉ

(1) A l'examen histologique des muscles de 15 cas de lupus la dégénérescence musculaire, légère ou modérée, fut constatée dans 73% des cas; des modifications similaires furent trouvées dans 37% des 30 témoins.

(2) Dans le lupus érythémateux la réaction vasculaire, qui est surtout veineuse, semble passer par trois phases: d'oedème, de réaction cellulaire et de sclérose. Ces modifications vasculaires dans les muscles et autour des nerfs dans le lupus sont identiques à celles que nous avons vues dans certains cas d'arthrite rhumatismale active. Il n'a pas été possible de déterminer le degré du rapport entre la dégénérescence musculo-nerveuse et les changes vasculaires et on ne peut pas dire si l'un est l'effet de l'autre ou bien si les deux phénomènes sont concomitants (simultanés) et dérivent d'une incitation commune. Les modifications vasculaires du tissu synovial étaient similaires à celles qu'on avait vues ailleurs. De plus, le stroma présentait de l'oedème initial suivi de la réaction fibroblastique aboutissant à la résolution de la fibrose. Seulement quelques cellules du revêtement synovial montraient de l'hyperplasie.

(3) La nature identique de la réaction vasculaire dans le lupus et de celle rencontrée dans l'arthrite rhumatismale active, ainsi que la similarité de cette réaction et de la réaction observée dans la périartérite noueuse est d'un grand intérêt et mérite des recherches ultérieures.

(4) Il n'a pas été possible de déterminer si les modifications que nous avons observées sont secondaires à une réaction produite par un facteur exogène ou bien si elles constituent le résultat d'une réaction hyperergique endogène.

Alteraciones Musculares, Nerviosas y Sinoviales en el Lupus Eritematoso

RESUMEN

(1) Al estudiar histológicamente los músculos de 15 casos de lupus se ha encontrado degeneración muscular, leve o moderada, en 73% de los casos; alteraciones similares fueron halladas en 37% de los testigos.

(2) En el lupus eritematoso la reacción vascular, principalmente venosa, parece transcurrir en tres fases: de edema, de reacción celular y de esclerosis. Estas alteraciones vasculares en los músculos y alrededor de los nervios son idénticas a las que hemos visto en ciertos casos de artritis reumatoide activa. No pudimos determinar el grado de relación entre la degeneración músculo-nerviosa y las alteraciones vasculares y no se puede decir si el uno es la consecuencia del otro o si ambos fenómenos son concomitantes (simultáneos) y proceden de un estímulo común. Las alteraciones vasculares del tejido sinovial se parecían a las que hemos visto en otra parte. Además, el estroma presentaba edema inicial, seguida de la reacción fibroblástica y luego de la resolución de la fibrosis. Sólo algunas células de revestimiento sinovial presentaban hiperplasia.

(3) La naturaleza idéntica de la reacción vascular en el lupus y de la reacción encontrada en la artritis reumatoide activa, así como la similitud con la reacción observada en la periarteritis nodosa da mucho que pensar y merece estudios ulteriores.

(4) No se pudo determinar si las alteraciones observadas resultan de una reacción producida por un factor exógeno o si constituyen el resultado de una reacción hiperérgica endógena.

NYLON ARTHROPLASTY IN RHEUMATOID AND OSTEO-ARTHRITIS*

BY

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We cannot foresee the time when early treatment of arthritis will prevent all articular damage and, consequently, all deformity about the joints (Hench and others, 1949). In spite of good nursing care and early splinting, occasionally severe injury to joints will occur. Without proper care, severe crippling is the common end-result. In chronic rheumatoid arthritis the greatest amount of crippling occurs in the lower extremity, and the knee joint shows the greatest disability. This begins with flexion deformity and progresses to subluxation, destruction of the articular surfaces, or ankylosis of the joint, Kuhns (1942).

The prevention and correction of these disabilities have always been serious problems, for when much damage has occurred, normal function is rarely regained. One of the most serious disabilities is ankylosis of the knee joint; while ankylosis in full extension does not interfere greatly with walking or standing, but is extremely awkward, and seriously disturbs rising and sitting. If both knees are stiff, it is often impossible for the patient to rise or dress himself without help.

Attempts have been made in the past to correct deformity and to produce motion in the knee joint stiffened by rheumatoid arthritis either by resection of the joint (Murphy, 1913) or by reshaping the articular surfaces and the interposition of fascia lata (Putti, 1920). In rheumatoid arthritis the tissues are defective, the bones are atrophied, the muscles are weak, and the fascia is thin, friable, and deficient in collagen, and rapidly wears away with use. Again, if adequate preparation and care have not been given to the patient an exacerbation in the arthritis may occur after operation.

Most of those who have reported upon arthroplasty of the knee have advised against its use in the presence of chronic arthritis (Samson, 1949), and our results up to 1940 had led us to a similar opinion. In twelve arthroplasties of the knee performed with the interposition of fascia lata, all soon became stiff again or had only a few degrees of painful motion of no practical value. The fascia lata soon disappeared and adhesions or bony ankylosis developed within the joint.

In our attempt to find a more durable substance for interposition between the articular surfaces after ankylosis from chronic arthritis, we asked the advice of the

* Read at the Annual Meeting of the American Rheumatism Association, San Francisco, Calif., June, 1950.

Polaroid Corporation of Cambridge, Mass. They provided five types of thin plastic membrane: polythene, butacite, pliofilm, ethocel, and two types of nylon. Small pieces of each of these plastic membranes were inserted into the rectus sheath of white rats. When the rats were sacrificed in one month in the course of other experiments, the tissues about the inserted membrane were examined. Little irritation was observed in the rectus sheath from any of these plastics; but no irritation was seen about the nylon membrane. Small pieces of nylon were then attached to the denuded under surface of the patella in rabbits. Here, also, no inflammation was observed in the joint and the animals seemed to use the knee in a normal manner. Necropsy showed practically no inflammation about the nylon. After studying methods of attaching the nylon to the periosteum or bone, it was used in the formation of new knee joints in patients with quiescent arthritis.

Nylon is the trade name for a synthetic base for rayon. Its chief commercial use is in the manufacture of tough, fine threads which are used for fabrics. Nylon thread has been used in surgery for many years and a number of reports have mentioned its inertness in tissues. Nylon is tough, moderately elastic and resistant to moisture and chemicals (Ingraham and others, 1947), but since it melts with heat, nylon membrane cannot be sterilized in the usual manner. It is most easily sterilized by immersion for 12 hours in a cold solution of bichloride of mercury, 1 to 1,000. For at least an hour before operation the nylon is soaked in sterile water or normal saline in order to remove as much bichloride as possible.

Operative Procedure

Our method of forming new knee joints is a simple one modified from that of Hass (1930). All the earlier students of this problem soon learned that intricate reconstruction of articular surfaces was a waste of time since the bone ends were greatly changed in shape by weight-bearing and by use. The knee joint is exposed by a long medial para-patellar incision. The patella is chiselled free from the femur, which, with the attached quadriceps tendon, is retracted laterally. The bony ankylosis between femur and tibia is chiselled away. The knee is then flexed. The lower end of the femur is fashioned into a rounded wedge transversely. A shallow groove is formed in the tibial plateau to fit the lower end of the femur. About one inch of the joint is resected in most instances, to permit unobstructed motion. The intercondylar notch is deepened for the patella. The patella is made thin and coin-like. All roughened areas are made smooth with a rasp. A single layer of nylon is sewed to the periosteum and bone of the femur covering all articular surfaces and the supra-patellar pouch. Pleats in the nylon are burned down smoothly with the electrocautery (Fig. 1).

In the postoperative care the leg is usually kept elevated upon pillows for 48 hours. Transfusions of one to two pints of blood are usually given as well as penicillin as prophylactic measures. The dressing is not changed for four or five days. Muscle-setting exercises are begun before the end of the first week after operation. Active exercises are begun after one week. Movement against gravity is begun as soon as the wound is healed. Weight-bearing with crutches and a plaster cylinder are begun in three weeks unless there is much bony atrophy. Resistance exercises (De Lorme and Watkins, 1948) are given to regain normal strength in the extensor muscles. Six months are usually required to regain normal strength and good function.

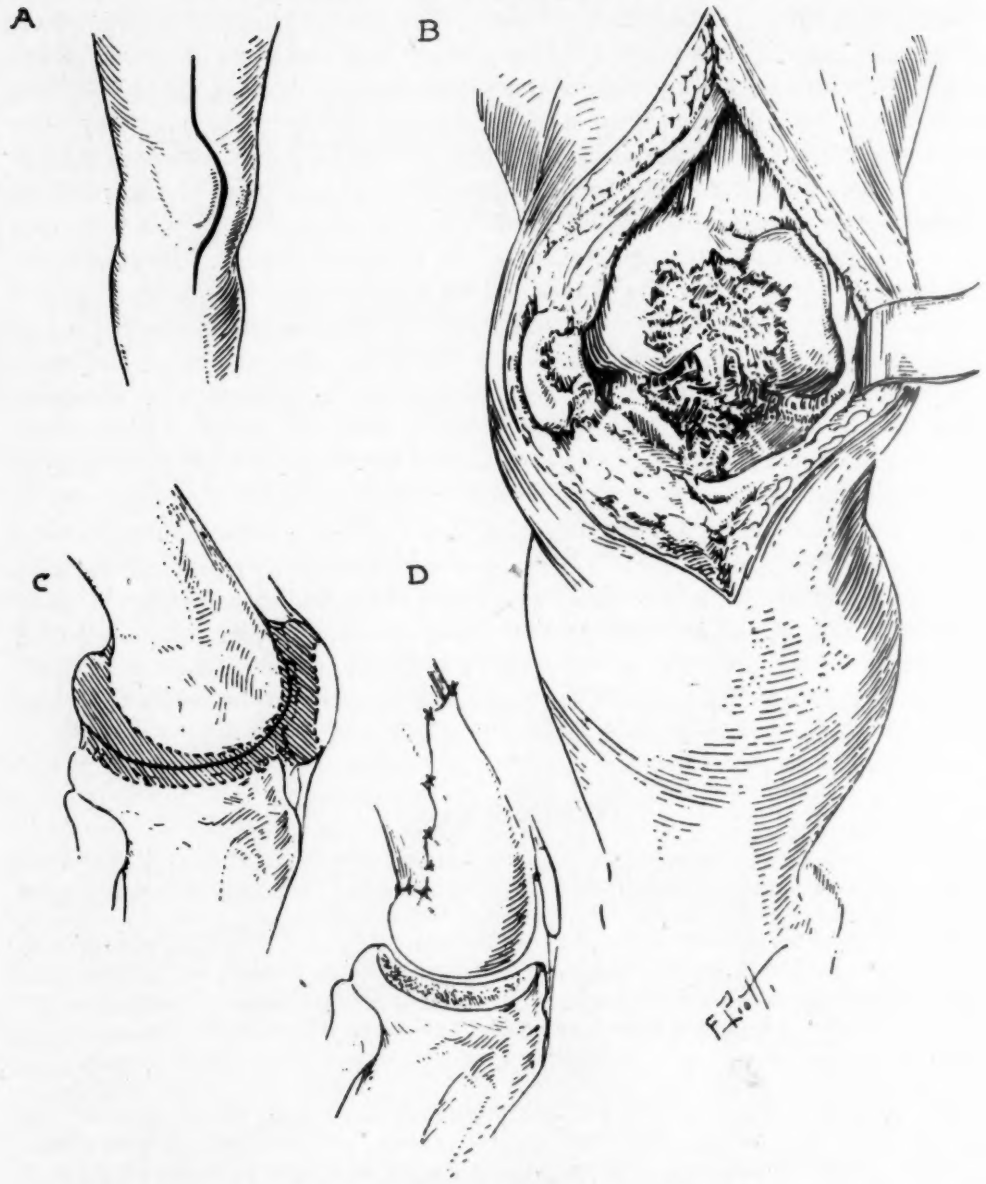

FIG. 1.—Sketches of operative procedure.
A. Incision.
B. Appearance of joint. The patella has been displaced.
C. Shaded area shows amount of bone removed.
D. Nylon attached to the periosteum at margins of femoral condyles.

Results

We have now employed this operation in thirty-three patients. Fourteen of them had bony ankylosis and nineteen had fibrous adhesions with destruction of the articular surfaces and limited painful motion in the joint.

Bony Ankylosis.—The operations upon the patients with bony ankylosis are summarized in Table I. All had rheumatoid arthritis, except one who had a suppurative arthritis followed by bony ankylosis of the knee joint. In the first six patients the knees were ankylosed in extension and we lengthened the rectus femoris tendon in order to permit the knee to flex 90°. Further experience taught us that such lengthening was unnecessary and that adequate flexion of the knee could be obtained without it.

We do not know when an arthroplasty of the knee can be considered an end-result. Our first patient was operated upon six and a half years ago. It usually requires about six months for the patients to obtain good function and to become free from all pain; in many patients we have observed a steady gain both in strength and in motion for a much longer period. In this group with bony ankylosis all obtained a satisfactory range of painless motion, except two: in one of these a slough

TABLE I
BONY ANKYLOSIS

Case			Date of Operation	Diagnosis	Knee	Preoperative Position	Postoperative Motion	Remarks
No.	Sex	Age						
1	F.	28	Jan. '44	Rheumatoid	Right	170°	180-90°	Quad. leng.
2	M.	30	Oct. '44	Rheumatoid Previous arthroplasty	Right	165°	0	Quadriceps slough
3	M.	22	Sept. '45	Rheumatoid Previous arthroplasty	Left	160°	180-85°	Quadriceps lengthening
4	F.	46	Apr. '46	Rheumatoid	Left	170°	170-155°	No pain
5	F.	30	June '46	Rheumatoid	Left	160°	180-80°	Quad. leng.
6	F.	22	May '47	Rheumatoid	Right	175°	180-110°	No pain
7	M.	20	July '48	Pyogenic	Right	175°	175-170°	Re-Op. 3/49 180-135° No pain
8	F.	24	Sept. '48	Rheumatoid	Left	180°	180-130°	Quadriceps Haemorrhage
9	F.	18	Oct. '48	Rheumatoid	Left	150°	180-120°	No pain
10	F.	47	Oct. '49	Rheumatoid	Right	150°	180-100°	No pain
11	F.	51	Nov. '49	Rheumatoid	Right	95°	180-90°	No pain
12	F.	54	Dec. '49	Rheumatoid	Left	140°	180-100°	No pain
13	F.	23	Jan. '50	Rheumatoid	Right	180°	180-120°	No pain
14	F.	30	Mar. '50	Rheumatoid	Left	180°	180-140°	No pain
15	F.	35	May '50	Rheumatoid	Left	170°	—	—

of the quadriceps muscle followed lengthening of the rectus femoris tendon; in the other extensive fibrous adhesions about the articular margins greatly restrict motion. We have now learned to avoid both these complications (Fig. 2 *a* and *b*).

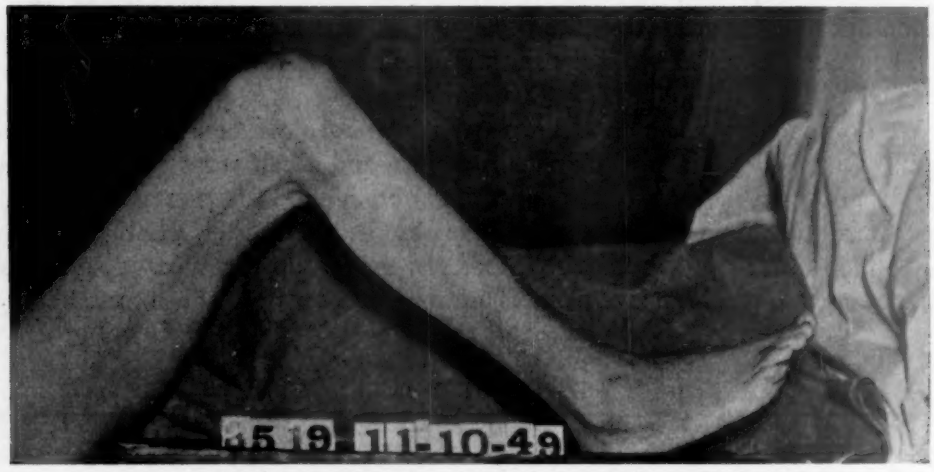

FIG. 2. (*a*).—Bony ankylosis of right knee of 20 years' duration.

FIG. (*b*).—Same knee 2 months after nylon arthroplasty. Superimposed photographs show active range of flexion and extension.

Other Conditions.—Arthroplasties have been found of value in a number of conditions besides bony ankylosis. In many patients the end-result is destruction of the joint with severe pain on motion and on weight-bearing. This is found in both rheumatoid and osteo-arthritis. In such knees there are two procedures available, arthrodesis or arthroplasty. Practically all the patients requested that an attempt should be made to obtain motion before the knee joint was stiffened by operation. We have operated upon eighteen knee joints which were destroyed and painful but still retained a small range of motion. In these joints, markedly

proliferated synovial tissues were removed, the degenerated intra-articular ligaments were excised, and irregularities and bony overgrowth were made smooth (Table II). In osteo-arthritis our experience with articular debridement alone has been disappointing; extensive reshaping of the articular surfaces is always necessary. Here the interposition of some substance is necessary to prevent intra-articular adhesions. We have hesitated to perform an operation of this magnitude upon patients over 60 years of age. Those with severe osteo-arthritis of the knee upon whom an arthroplasty has been performed have now a wide range of painless motion, and we believe that the operation will have a wider application in severe osteo-arthritis.

TABLE II
FIBROUS ADHESIONS, DESTRUCTION OF JOINT

Case			Date	Diagnosis	Knee	Preoperative Motion	Postoperative Motion	Remarks
No.	Sex	Age						
1	F.	54	Oct. '45	Rheumatoid	Right	180-170°	170-100°	No pain
2	M.	42	July '47	Rheumatoid	Left	150-130°	170-110°	Temporary sinus
3	M.	64	Feb. '48	Rheumatoid	Left	180-170°	180-120°	Slight pain
4	F.	53	Mar. '48	Rheumatoid	Right	180-100°	180-75°	No pain
5	F.	16	May '48	Rheumatoid	Right	160-150°	175-85°	No pain
6	M.	28	Dec. '48	Pyogenic	Right	170-160°	180-140°	Pain
7	M.	47	Jan. '49	Rheumatoid	Right	165-95°	180-85°	No pain
8	M.	54	Feb. '49	Rheumatoid	Left	160-130°	180-95°	No pain
9	F.	54	Apr. '49	Osteo-arthritis	Left	170-95°	180-80°	No pain
10	F.	51	May '49	Rheumatoid	Left	155-130°	180-110°	No pain
11	M.	48	Sept. '49	Rheumatoid	Left	170-100°	180-110°	No pain
12	F.	48	Nov. '49	Osteo-arthritis	Left	170-155°	180-90°	No pain
13	M.	44	Dec. '49	Osteo-arthritis	Right	170-95°	180-90°	Nylon loosened Slight pain
14	F.	40	Jan. '50	Rheumatoid	Right	170-155°	180-100°	No pain
15	F.	49	Jan. '50	Rheumatoid	Left	165-120°	180-110°	No pain
16	F.	55	Feb. '50	Osteo-arthritis	Right	160-135°	180-90°	Slight pain
17	F.	28	Mar. '50	Rheumatoid	Left	150-110°	180-130°	Slight pain
18	M.	42	May '50	Rheumatoid	Right	155-100°	Procedure not yet complete	
19	F.	40	May '50	Rheumatoid	Left	185-160°	"	
20	F.	40	May '50	Rheumatoid	Left	185-90°	"	

Discussion

Arthroplasty of the knee in chronic arthritis is always an operation of election. It does not produce a normal knee joint but usually results in a useful joint with a fairly wide range of painless motion. We believe that these joints, like those which have been operated upon with the interposition of fascia lata, will eventually wear out; but to date none of those we have treated have shown any functional deterioration.

There are no definite indications, but there are a few contraindications to arthroplasty. The chronic arthritis should be quiescent clinically. Local arthritic activity is sometimes confused with mechanical irritation of the joint. The other joints which have had arthritis should show no heat, swelling, or pain on motion. The general condition of the patient should be good in order to withstand an operation of this magnitude without danger. The patient should be co-operative and psychologically well adjusted. In children no arthroplasty should be performed until the epiphyses have closed, for operation upon an actively growing epiphysis will shorten the limb considerably. If there is much crippling there should be a definite plan of rehabilitation designed to correct the proximal joints before the more distal ones. There should be sufficient funds available for the necessary preoperative and postoperative care.

With our limited experience we feel that arthroplasty in chronic arthritis is indicated:

(1) *In bony ankylosis of the knee when there is a fair range of motion in the hip joints.* If the hips are stiff they should be mobilized before operation on the knee is contemplated. If both knees are ankylosed both can be operated upon, but at least a year should elapse between the two operations. In order to make walking possible, normal strength should be present in the first knee before the second knee is mobilized.

(2) *In knee joints which have been severely damaged with resultant limited motion and painful weight-bearing.* The articular damage is always found to be more severe at operation than the *x*-ray and the clinical examination would suggest. In a number of patien's the operative procedure contemplated was synovectomy or removal of loose bodies and bony spurs, but in many instances extreme pannus formation, erosion and irregularity of the articular cartilages, and widespread adhesions with obliteration of the articular cavity forced us to construct a new joint in order to make articular function possible.

(3) *In severe osteo-arthritis, whether primary or secondary, when there is extreme articular damage and no response to conservative therapy.* Our experience both with debridement and with arthrodesis has been disappointing. With debridement alone, pain and increasing stiffness have soon recurred, as one would expect unless the underlying mechanical derangement had been corrected. Arthrodesis of the knee in osteo-arthritis has soon led to similar pain in the ankle, hip, and low back. Relief of this degenerative process in any joint is dependent upon a nearly normal axis of motion in the joint and a normal line of weight-bearing which can be helped more effectively by arthroplasty than by any other known operative procedure.

In operations of this nature the postoperative period is most important, since motion depends upon the avoidance of complications and the early and persistent activity of the patient. The patient must begin motion or muscle-setting procedures

within a few days, and active and resistance exercises of increasing strenuousness must be performed after wound-healing to secure good motion and normal strength. In a few patients normal strength and good function have gradually come after a year and a half, but we do not advocate such slow convalescence; adhesions and muscular stiffness can develop too readily.

The desideratum after arthroplasty of the knee has changed little in the last 50 years: it is a stable, painless knee with about 60° of motion. In a recent review, Speed and Trout (1949) stated that 70° of motion made for the greatest endurance and stability, but many of our patients have over 90° of motion and all of them are stable and painless. The greater range of motion, we believe, has resulted from the vigorous use of the newer physiotherapy techniques, particularly resistance exercises. Stability is chiefly the result of sparing the collateral ligaments and developing the musculature about the knee.

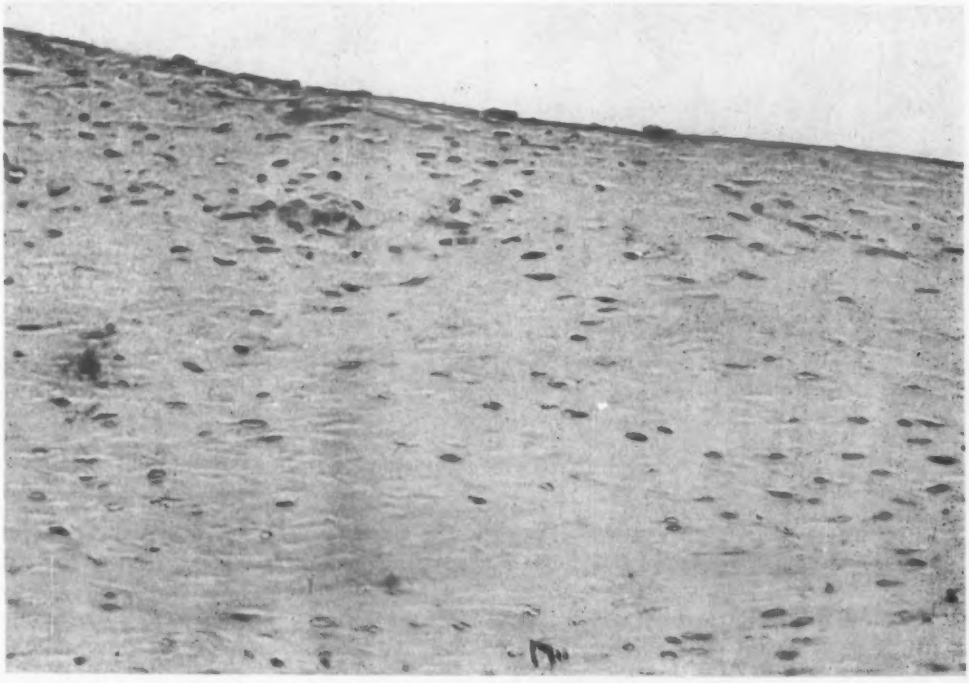

FIG. 3.—Tissue on femoral condyle beneath nylon membrane. There is no reaction to the nylon, and fibrous tissue forms a flattened layer beneath it.

The changes which occur in knees after nylon arthroplasty have been observed in *x* rays and by re-operation in three patients. The changes are similar to those reported by Campbell after fascial arthroplasty, but adhesions are rare after nylon (Fig. 3). There is little postoperative effusion. After a few weeks the aspirated fluid resembles normal joint fluid. After walking in the presence of osseous atrophy, a little flattening occurs in the lower end of the femur, but as far as can be determined this does not interfere with the range of motion. In about four months the moving articular surfaces under the nylon become covered with a firm layer of

fibrous tissue which resembles fibrocartilage. The soft tissues about the nylon undergo mild proliferation, but there is no definite inflammation. If the nylon becomes detached (this occurred in two patients), the symptoms of articular derangement and osseous and fibrous-tissue proliferation recur. No changes are observable after six months.

Summary

In patients with bony ankylosis or severe articular damage in chronic arthritis a useful range of painless motion can usually be obtained by arthroplasty with nylon membrane.

To date we have observed no reaction to the nylon membrane.

A firm layer of fibrous tissue develops under the nylon.

Careful postoperative attention is required to prevent complication and early active motion is essential to the success of this procedure.

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Discussion

DR. PHILIP LEWIN (*Chicago, Ill.*): This is very interesting material. Duncan McKeever started using cellophane, and we began using nylon in 1943 at the Mayo General Hospital. Be sure to differentiate nylon sheeting from nylon fabric. This material is sheeting, and it works.

We reported on some of our work at the 6th Service Command Conference in 1944. We put nylon sheeting into skulls to replace the dura, and after eight or ten weeks it could be removed, washed, sterilized, and used over again. There was no reaction by the host tissues nor any reaction by the material upon the host tissues. We used it round tendons, nerves, and blood vessels. It is very interesting that you can seal it by a warm haemostat. If you have the haemostat warm enough, you can pinch it and seal it, just as little popcorn bags are sealed. When you put it round a structure such as a tendon and have a little sticking out, you can seal it with a couple of snaps so that sutures need not be used.

I hope, in closing the discussion, Dr. Kuhns will tell us how he secures it to the bone, because it is so difficult to attach this material by suture.

DR. KUHNS: The cellophane was originally 0·003 in., but now they are making it 0·006 in. thick. Both materials work equally well, although the 0·003-in. material is a little more elastic and easier to handle. It is secured from the Plastics Division of DuPont, and it costs $3.83 per pound. One pound comes one foot wide and about three yards long. It will do a great many operations.

It is sutured either to the periosteum or to the bone. In two patients we did not fasten the nylon securely to the periosteum or to the bone, and it started to roll and gave us the same symptoms as internal derangement or torn cartilage. In those two patients we simply left it in place for 5 months and then removed it.

Arthroplastie au Nylon dans l'Arthrite Rhumatismale et dans l'Ostéo-arthrite

RÉSUMÉ

Dans des cas d'ankylose osseuse ou de lésion articulaire grave due à l'arthrite chronique on obtient généralement un mouvement indolore et d'amplitude utile après l'arthroplastie avec une membrane de nylon.

Jusqu'à présent nous n'avons pas observé de réactions dues à la membrane de nylon.

Une couche compacte de tissu fibreux se développe sous cette membrane.

Un traitement post-opératoire soigneux est nécessaire pour éviter des complications et le mouvement actif précoce est essentiel pour que ce procédé réussisse.

Artroplastia con Nylon en la Artritis Reumatoide y en la Osteo-artritis

RESUMEN

En casos de anquilosis ósea o de lesión articular debida a la artritis crónica grave se puede obtener generalmente movimientos sin dolor de amplitud útil por medio de artroplastia con una membrana de nylon.

Hasta ahora no hemos observado reacciones debidas a la membrana de nylon.

Una capa firme de tejido fibroso se desarrolla debajo de esta membrana.

Para evitar complicaciones hay que tratar a los enfermos con mucho cuidado y el movimiento activo temprano es preciso para el éxito del procedimiento.

PREGNENOLONE IN THE TREATMENT OF RHEUMATOID ARTHRITIS

BY

G. NORMAN MYERS

Regional Medical Research Centre, Royal Bath Hospital, Harrogate

Since Hench, Kendall, Slocumb, and Polley (1949) described their results from the administration of cortisone (17-hydroxy-11-dehydrocorticosterone) and of the anterior pituitary adrenocorticotrophic hormone in the treatment of rheumatoid arthritis, there has been much speculation regarding the possible use of other substances which might produce similar effects. The search for such substances has been confined primarily to two main groups:

(*a*) those, like adrenaline, which are known to stimulate the production of the anterior pituitary corticotrophic hormone,
(*b*) those which may be precursors of more active steroid hormones.

From the chemical standpoint △-5-pregnenolone has been suggested as a precursor and has attracted the attention of a number of workers.

Davison and others (1950) treated thirty arthritis patients with pregnenolone acetate, fourteen of whom were suffering from rheumatoid arthritis. Solutions in oil, as well as aqueous suspensions, were administered by the intramuscular route. Daily injections, up to 200 and 300 mg. respectively, were given over a period of 3 to 8 weeks. They reported results which appear to be definitely favourable. Pain and stiffness in joints was diminished, muscle strength was increased, and fatigue was less evident. A feeling of "well-being" was established, usually within a few days. Reduction in joint swelling was slow, and reduction in the erythrocyte sedimentation rate, if any, did not run parallel with the clinical improvement, but followed it. No toxic effects were observed; the menstrual cycle and sexual potency were unaffected. None of the subjects under test experienced euphoria, but one patient suffered from insomnia while receiving the maximum dosage. When the injections were discontinued, the arthritic symptoms returned within a few days. No beneficial effects were observed in cases of rheumatoid arthritis with psoriasis, severe gout, or disseminated lupus.

Ishmael and others (1949) employed pregnenolone in doses up to a maximum of 100 mg. daily, as well as in combination with high-dosage androgen and oestrogen therapy. They reported that when pregnenolone was administered alone, about 50 per cent. of the patients with rheumatoid arthritis responded favourably. One patient, however, developed mental depression and a feeling of weakness.

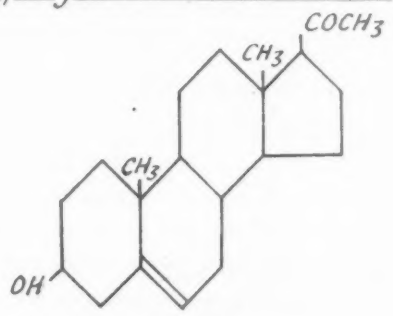
Freeman and others (1950) also describe improvement following the administration of pregnenolone. Thirty patients suffering from rheumatoid arthritis were given pregnenolone, or pregnenolone acetate, orally over a period of six weeks, the daily dose being 500 mg. Of these patients 50 per cent. showed a decided improvement, and another 30 per cent. showed some degree of amelioration of symptoms. The remaining 20 per cent. showed no change. Of sixteen subjects in whom treatment was discontinued, improvement was maintained for an average period of six weeks. No toxic effects were observed.

Guest and others (1950) administered pregnenolone by the intramuscular route daily, or two or three times weekly, to nineteen patients. Seventeen cases of rheumatoid arthritis showed no improvement; one patient with rheumatoid spondylitis improved objectively and subjectively, and another showed minor subjective improvement at the end of one week's treatment, which was followed by a relapse in spite of continued therapy. Stock and McClure (1950), who treated ten cases for 2 weeks with a daily dose of 200 mg., reported an objective improvement in three cases.

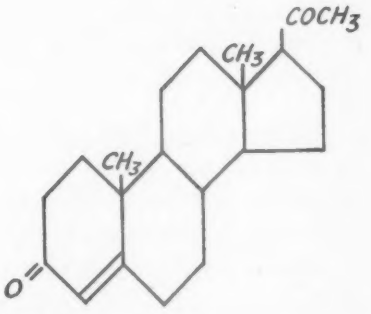
Copeman and others (1950) studied the effect of pregnenolone on eight cases of polyarthritis of the rheumatoid type. A uniform dose of 300 mg. per day was employed for nine days. No significant change was recorded other than an unexplained rise in pregnanediol excretion on the 7th day. The erythrocyte sedimentation rate rose during treatment.

It has been suggested that pregnenolone may be an intermediate substance in the synthesis and metabolism of certain steroid compounds present in the body. It has been isolated from the testes of the hog by Ruzicka and Prelog (1943), and is thought by some to be a precursor of testosterone as well as of progesterone.

△-5-pregnen-3(β)-ol-20 one



Pregnenolone



Progesterone

So far it has not been isolated from human sources (Tyler, 1949). It can be synthesized from cholesterol and stigmasterol by oxidation of the C_{20} side chain. By suitable oxidation, pregnenolone can also be converted into dehydroisoandrosterone, deoxycorticosterone, or progesterone. These oxidative conversions can be performed *in vitro*, but no evidence has so far been produced to show that they can take place in the body. Hoagland (1944) claimed that the daily administration

of 25 to 27 mg. pregnenolone to factory workers augmented their physical output by about 18 per cent. This dosage was well tolerated and no secondary effects were observed. Gasche and Schuler (1946), using rats, report an absence of oestrogenic effects with doses up to 200 mg./kg. A progesterone-like action on castrated rabbits was observed by Miescher and Gasche (1943).

Methods

All the subjects selected for this investigation were in-patients showing definite signs of rheumatoid arthritis in more than one joint. The duration of the disease varied in the different subjects and the severity of the condition was assessed in accordance with the therapeutic criteria and related aids in rheumatoid arthritis recommended by the American Rheumatic Association (Steinbrocker and others, 1949).

For the purpose of the present investigation it was thought desirable to study the long-term effects of pregnenolone, in addition to some short-term effects, and it was decided to vary the individual dosage and the period of administration over wide limits. The dosage employed varied between 10 and 300 mg. per day, and the periods of administration ranged from 5 to 44 days. In most cases the pregnenolone was given in solution as an intra-muscular injection into the upper and outer quadrant of the buttock. In a few cases the injections gave rise to pain; this was most evident where a large dosage was employed. Whenever this occurred, the intramuscular dose was reduced and the balance given in the form of sublingual tablets. In two cases the sublingual route was used exclusively during the whole of the trial period.

Estimations of the erythrocyte sedimentation rate (E.S.R.) by the Spa Hospitals Method, plasma viscosity, packed-cell volume, erythrocyte and leucocyte counts, eosinophil count, and haemoglobin were made during the two days preceding the administration of pregnenolone, during the period of administration, and for at least one week after the drug had been discontinued.

All the subjects received routine physiotherapy throughout the whole period. In order to avoid psychological effects, they were informed that they were not receiving cortisone or ACTH, but that the substance under test was part of a clinical trial to ascertain any blood changes which might follow its use. Throughout the trial it was obvious that they did not expect anything to happen, at least, anything which they would be able to observe. All other drugs were withheld during the period covered by the trial.

Assessment of Clinical Effects

Observations were confined to those effects which might be expected to give as clear-cut an answer to the problem as possible. They were based on both subjective and objective observations, in addition to results obtained in the clinical laboratory. The range of joint-movement, power of hand grip, etc., were recorded.

Five male and five female in-patients were selected. In three subjects the disease appeared to follow direct injury to the body, though not necessarily to the joints affected. A brief outline of each case is given.

After examination they were graded according to the recommendations of Steinbrocker and others (1949); as may be seen in Table I, the ages varied from 15 to 50 years, and the duration of symptoms from 8 months to 10 years. The gradings were unaltered by the use of pregnenolone.

Table II shows the dosage of pregnenolone employed and the frequency and duration of administration in each case. Total dosage varied from 0·09 g. given over a period of 9 days to 12·3 g. in 41 days.

TABLE I

CLASSIFICATION OF CASES

(*American Rheumatic Association Code*)

Patients				Before Pregnenolone		After Pregnenolone	
Case No.	Sex	Age (years)	Duration of symptoms (years)	Stage (progression)	Functional capacity	Functional capacity	Response (grade)
1	F	15	2½	2	2	2	3
2	F	18	3	3	3	3	4
3	M	33	12	3	4	4	4
4	M	38	2½	1	2	2	3
5	M	25	8 mths	2	2	2	3
6	F	25	8 mths	1	2	1	3
7	M	37	1	2	2	2	3
8	F	24	7	3	2	2	3
9	F	23	5	2	2	2	3
10	M	50	9	3	3	3	4

TABLE II

DOSAGE, E.S.R., AND PLASMA VISCOSITY

Case No.	Sex	Dosage					Sedimentation rate (per cent.)		Plasma Viscosity	
		Amount (mg.)	Route	Frequency	Duration (days)	Total Administered (g.)	Before Pregnenolone	After Pregnenolone	Before Pregnenolone	After Pregnenolone
1	F	200	oral	daily	40	8	16- 8	13- 7	20·3	20·0
2	F	100	intramuscular	daily	5	0·5	42-44	42-39	21·6	20·9
3	M	100	intramuscular	daily alternate days	9 22 } 31	2	52-43	51-41	25·2	22·4
4	M	300	intramuscular	daily	23	6·9	36-37	46-44	22·0	21·8
5	M	300 100 200 300 100 200	intramuscular intramuscular oral intramuscular oral intramuscular	daily daily daily daily	7 13 8 } 41 13	2·1 3·9 2·4 } 12·3 3·9	48-43	 50-44 45-45	22·4	 21·4 22·6
6	F	300 300	intramuscular oral	daily daily	22 18 } 40	6·6 5·4 } 12·0	46-43	50-44 47-42	24·2	23·2 23·4
7	M	300	oral	daily	36	10·8	16-16	20-23	18·2	19·2
8	F	30	intramuscular	daily	8	0·24	32-21	32-26	21·4	21·3
9	F	10	intramuscular	daily	9	0·09	25-17	27-16	19·8	19·1
10	M	10 60 150 300	intramuscular intramuscular intramuscular oral	daily daily alternate days daily	14 7 12 21 } 54	0·14 0·42 1·80 6·30 } 8·66	21-21 24-22 40-40	21-22 24-22 45-43	19·2 22·2 20·0	22·2 19·0 21·5

Examination of the erythrocyte sedimentation rates and plasma viscosity shows little or no change as a result of pregnenolone administration except in Cases 4, 7, and 10. Case 4 showed an increased sedimentation rate without any alteration in plasma viscosity. A similar increase was seen in Case 7, here the viscosity was also slightly increased. Case 10 is particularly interesting; here there was no change

until the 21st day, when the E.S.R. showed a remarkable increase. The plasma viscosity followed a similar but less spectacular course.

No changes in E.S.R. or plasma viscosity were recorded in seven out of ten cases; the other three cases all showed an increase in sedimentation rate.

During this period the clinical results showed a remarkable agreement with the results set out above. No patients showed any change in their condition except Cases 4, 7, and 10. All three complained of increased pain and stiffness in the affected joints five to seven days before the E.S.R. increase was recorded. In Cases 4 and 7 this was not nearly so marked as in Case 10.

The increased pain was not accompanied by any joint swelling, but in Case 10 the pain was so severe as to keep him awake at night unless given special analgesic medication. He had a high threshold for pain, and rarely complained even when it was very severe, but movement of the joints at this stage produced wincing. There was redness and swelling around the joints.

The leucocyte and eosinophil counts before and after pregnenolone only are set out in Table III. The intermediate counts, which showed nothing decisive, have been omitted. No conclusive results can be drawn from these figures. The high eosinophil counts seen in Cases 1, 3, 6, and 10 bore no relationship to the severity of activity of the disease. The counts, before the administration of pregnenolone, of Cases 1 and 2 might be taken as an example. Case 2 had a lower eosinophil count than Case 1, and yet the arthritic condition was much worse. On the other hand, Case 10, having the highest eosinophil count, had the disease in a more actively acute stage and, in this respect, was worse than any of the others.

TABLE III
BLOOD COUNT

Case No.	Before Pregnenolone		After Pregnenolone		Total Dosage	
	Eosinophils (per c.mm.)	Leucocytes (thousands)	Eosinophils (per c.mm.)	Leucocytes (thousands)	days	g.
1	155	8·2	45	7·4	40	8
2	50	8·3	80	8·2	5	0·5
3	200	7·2	220	7·5	30	2
4	110	11·4	175	7·8	23	6·9
5	90	6·2	—	6·9	41	12·3
6	200	11·0	—	8·4	40	12·0
7	80	5·7	145	7·0	36	10·8
8	130	6·0	100	6·5	8	0·24
9	140	5·0	145	8·0	9	0·09
10	530	6·4	190	8·2	54	8·66

The leucocyte counts showed no constant change in response to pregnenolone. In five cases they were substantially the same before and after pregnenolone; two cases showed a marked reduction, and three showed a slight increase.

The results of the erythrocyte counts, haemoglobin and packed-cell volume determinations are set out in Table IV which shows no significant alteration in any of these totals after pregnenolone therapy.

TABLE IV
BLOOD EXAMINATION

Case No.	Stage	Red-Blood Cells (millions)	Haemoglobin (per cent.)	Colour Index	Packed-Cell Volume (%)
1	Before	4·7	78	0·83	36
	After	4·4	80	0·87	37
2	Before	5·4	90	0·84	44
	After	5·0	82	0·82	40
3	Before	4·7	66	0·70	36
	After	4·6	64		35
4	Before	6·1	90	0·74	43
	After	6·0	84		41
5	Before	4·9	78	0·82	39
	After	5·1	80		42
6	Before	5·2	82	0·79	40
	After	5·0	80		39
7	Before	5·2	100	0·96	42
	After	5·2	100	0·96	45
8	Before	4·5	74	0·83	35
	After		78		38
9	Before	4·6	83	0·9	37
	After	4·1	76	0·92	35
10	Before	4·4	85	0·97	42
	After	4·9	90	0·92	41

Unfortunately the eosinophil response to adrenaline was assessed in only four cases (Table V). One showed a marked reduction in circulating eosinophil cells, and another a slight response, but the other two showed no change.

TABLE V
EOSINOPHIL RESPONSE TO ADRENALINE

Case No.	Sex	Age (years)	Duration of Symptoms (years)	Eosinophils per c.mm.	
				Before adrenaline (10 a.m.)	After adrenaline (2 p.m.)
3	M	33	12	220	175
4	M	38	2½	175	164
6	F	25	8 mths	200	200
8	F	24	7	130	45

Case Reports

Case 1. Female, aged 15 years.—Two and a half years ago she experienced pain in both legs, which was quickly followed by swelling of the ankles. Four months later the finger joints became affected and the wrists were soon involved. The condition is said to have dated from the onset of menstruation. There is no family history of rheumatoid arthritis.

The hands and feet are cold and moist and subject to chilblains. The onset of the disease was afebrile, acute, and polyarticular.

Examination.—The interphalangeal joints of both hands show fusiform swelling and the wrists are swollen. The feet are painful and swollen at the first metatarso-phalangeal joints. The ankles are also slightly swollen. Nothing abnormal was found in the respiratory, cardio-vascular, urinary, or nervous systems. Digestion is good. Blood pressure 110/74 mm. Hg.

X-Ray Examination.—The carpal bones show osteoporosis. There is a definite narrowing of the joint spaces in both wrists, which is most marked in the os magnum and semilunar bone of the left wrist and the radiocarpal in the right wrist. There is general osteoporosis of the bones in the feet. The ankle joints appear to be normal.

Laboratory Findings.—Serum colloidal gold reaction—positive (5); B.M.R. +6 per cent.; creatinine in urine 1·25 mg. per 100 ml.

Therapy.—200 mg. pregnenolone were given orally for 40 days. Clinical examination during the period of administration showed no definite evidence of improvement in her condition. She continued to have pain in both hands, especially in the early morning when she awakened. The pain in the ankles varied from day to day, but was always worse when she walked. The pain in the right shoulder, however, became much easier. Her general health improved and she gained in weight. Three weeks after the pregnenolone had been stopped, she believed that she was walking a little better and with less pain. *X* ray revealed no change in the condition of her joints.

Case 2. Female, aged 18 years.—The disease commenced two and a half years ago with pain and swelling of the right foot. Within a few months the left foot and left knee were affected. A few months before the onset of the disease she fell on some rocks and cut the dorsum of her right foot. The lesion healed very slowly and signs of rheumatoid arthritis were evident shortly afterwards. The onset was insidious and afebrile, and affected one joint only. There is no family history of rheumatic disease.

Examination.—Nothing abnormal was found in the respiratory, nervous, or urinary systems. The blood pressure was 105/55 mm. Hg. The second pulmonary sound was accentuated and a soft diastolic murmur was present along the left sternal border. The heart was normal in size. The appetite is poor. Her weight was 6 st. 5 lb., being normally 7 st. 1 lb. There was limitation of the movements of both ankles, with pain on movement. All movements of the hip joints were minimal. Abduction of the feet was only about three to four inches and even this was accomplished with great pain. She found walking difficult, not only because of the pain in her hip joints, but because of an added pain in the groin and lumbar region. There was marked wasting of the muscles of both thighs and legs. The left knee was swollen and painful when moved.

X-Ray Examination.—Both ankles and feet show advanced rheumatoid changes in addition to marked calcaneal spurs on both heels. Both knees show generalized bone rarefaction with stencilling of the outlines such as is seen in the early phase of rheumatoid arthritis. The hip joints show early signs of arthritis. The spinal curves are deficient, the disk spaces appear normal.

Laboratory Findings.—Serum colloidal gold reaction—negative; B.M.R. +22 per cent.; creatinine in blood 0·5 mg. per 100 ml.

Therapy.—100 mg. pregnenolone were given intramuscularly for 5 days. No change in her clinical condition was observed during the period of administration. Three weeks later she had less pain in her hips and was walking a little better. The improvement was not very marked, nor was it sustained.

Case 3. Male, aged 33 years.—Twelve years ago he experienced a feeling of very marked fatigue after a long motor journey. A few days later, after swimming, he had a sudden pain in the joints of both great toes. He continued to work for three months in spite of a painful limp, before being seen by an orthopaedic surgeon who diagnosed pes planus. Later he was sent to hospital as a case of rheumatoid arthritis and treated with protein shock and gold therapy. The results were disappointing. For some years the pain and swelling of the joints continued and, in time, the metacarpo-phalangeal joints of both thumbs became involved. Slowly the condition became quiescent until two years ago when the right shoulder became involved. During the past six months he has developed

stiffness in both mandibular joints and in the lumbo-sacral region. The left knee has become swollen and painful and he has lost about 1 st. in weight during the past three months. The onset of the arthritis was acute, afebrile, and polyarticular. His family history is particularly interesting; two brothers died in childhood with rheumatic fever, and one sister had rheumatic fever as a child.

Examination.—There is swelling of the carpal and metacarpo-phalangeal joints of each thumb, both joints are ankylosed. The ankles are slightly swollen with tenderness over the heads of the metatarsals. The spine shows limited movement throughout. His normal body weight was 10 st., but he now weighs 7 st. 12½ lb. The chest has a poor expansion (1¼ in.), and there is dyspnoea on exertion. *X*-ray examination shows a fair degree of lung fibrosis, especially on the right side, but there is no evidence of any active lesion. The digestive, nervous, urinary, and cardiovascular systems are normal. The blood pressure, 106/78 mm. Hg, is low. There is sweating of the hands and feet, but no evidence of any marked peripheral vascular disturbance.

X-Ray Examination.—There are signs of bilateral sacro-iliac arthritis and osteoporosis of the lumbar vertebrae and slight scoliosis of the upper dorsal spine, with narrowing of the disk space at the level of the 4th and 5th cervical vertebrae. The right shoulder and the metatarso-phalangeal joints of both feet show advanced arthritic changes.

Laboratory Findings.—Serum colloidal gold reaction—positive (5).

Therapy.—100 mg. pregnenolone were given intramuscularly for 9 days, when it was reduced to alternate days because of a slight rise in temperature to 99° F. which lasted 2 days. The injections were continued on alternate days for 22 days. No alteration in his clinical condition was observed. His weight remained constant at 8 st.

Case 4. Male, aged 38 years.—In February, 1948, he noticed swelling of the fingers which was soon followed by joint stiffness and pain. In April, 1950, his knees became affected and a month later his left shoulder and elbows became very stiff. Although the stiffness diminished, he has had intermittent pain in the left arm since then. No other members of his family have had rheumatism.

Examination.—The proximal interphalangeal and metacarpo-phalangeal joints of both hands are swollen. The wrists are stiff and painful. There is pain and tenderness over the metatarsal heads of both feet. His present weight is 11 st., 2 st. having been lost during the past 18 months. There were no signs of any marked peripheral vascular disorders.

Laboratory Findings.—Serum colloidal gold reaction—negative; B.M.R. +5 per cent.

Therapy.—300 mg. pregnenolone were given intramuscularly for 23 days. Seven days after the injections were started, he became distinctly cheerful and announced that the pain and stiffness had completely disappeared from his hands and that he had less pain in the feet. On the 21st day he stated that he had no pain in any of his joints, that the joints did not feel so stiff, and that they moved more freely. Clinical examination showed no alteration in the range of the joint movements, but an almost complete absence of joint pain. When discharged from hospital on the 34th day, he said that he was still free from joint pain and stiffness and was pleased at the progress he had made.

Case 5. Male, aged 25 years.—Acute onset in January, 1950, one week after an accident to his left hand. The left index finger became swollen and pain commenced in the proximal interphalangeal and metacarpo-phalangeal joints and in the left wrist. One week later the left knee became affected and on the following day the right ankle became painful. Within a few days the right knee became involved and after a further three weeks the right shoulder and both wrists were swollen and painful. Three weeks ago slight swelling and redness around the interphalangeal joint of the left great toe and the left temporo-mandibular joint became evident. The onset of the disease was febrile, acute, and monarticular. His recent past history reveals treatment of psychoneurosis with insulin shock therapy. There is nothing of interest in his family history.

Examination.—He is a big, broad-shouldered type, and somewhat adipose. There is a fusiform swelling of the left 3rd metacarpo-phalangeal joint. The 1st metatarso-phalangeal joints

of both feet are painful and tender to pressure. The left temporo-mandibular joint and the right sterno-costal joints are tender.

X-Ray Examination.—The internal femoral condyles of both knees show in their lateral views, rarefaction of bone beneath the articular surfaces. There is generalized osteoporosis, particularly in the tarsus of the right foot.

Laboratory Findings.—Plasma uric acid 3·6 mg. per 100 ml.; B.M.R. +10 per cent.

Therapy.—He was started on a daily intramuscular injection of 300 mg. pregnenolone. On the 7th day he complained of pain in both buttocks at the site of the injections. The daily injection was then reduced to 100 mg. and the balance of 200 mg. was given in tablet form by the sublingual route. This method of administration was continued for the next 13 days, when the intramuscular route was again resorted to. At the end of a further 8 days it was again found necessary, because of pain, to reduce the daily intramuscular injection to 100 mg. and to give the balance of 200 mg. in sublingual tablets. Objectively there was no material alteration in his clinical condition during the first 8 days on pregnenolone. He still complained of pain and stiffness in both hands and knees, although his general manner was more cheerful. On the 10th day he stated that there was a great reduction in the pain in the affected joints, particularly in the feet and knee joints. At this time, however, the hands began to show swelling over the length of the metacarpal bones of both hands, especially the left. By the 15th day the feet and knees showed further improvement while the left hand showed signs of inflammation of the 3rd metacarpo-phalangeal joint which was hot, tender, swollen, and inflamed. On the 21st day his general health had improved appreciably. There was less pain in the hands, but more in the feet. On the 36th day the 3rd and 4th metacarpo-phalangeal joints were still very painful, but less swollen, and there was less pain in the knees and feet than at any time since the investigation was started. He had gained 2 st. in weight since his admission to hospital 2 months earlier. His left hand was still swollen and painful on the 50th day, when he discharged himself.

Case 6. Female, aged 25 years.—In January, 1950, she complained of pain, fatigue, and swelling of the right ankle. The left foot and ankle were soon involved and later the knees, shoulders, and wrists. More recently the hands became affected. For three months the disease progressed slowly, but then became more acute. By June she was unable to follow her employment. The onset was afebrile, insidious, and polyarticular. The family history shows no evidence of rheumatoid arthritis.

Examination.—There is a malar flush. The patient is slightly obese, but there is evidence of recent loss of body weight. Her present weight is 10 st. 11 lb. (previously 13 st.). The hands show slight fusiform swellings of the proximal interphalangeal joints. The metatarso-phalangeal joints of both feet are tender and painful, as well as the ankles. The respiratory, digestive, urinary, and nervous systems appear normal. The cardiovascular system revealed nothing of importance. The hands and feet were cold and sweaty.

X-Ray Examination.—There is slight osteoporosis of the left knee joint in addition to the tarsal and other bones of both feet. The plantar arches are dropped.

Laboratory Findings.—Serum colloidal gold reaction—positive (3); B.M.R. +1 per cent.

Therapy.—300 mg. pregnenolone were given intramuscularly for 22 days, when pain, tenderness, and signs of inflammation developed at the sites of the injections. The injections were discontinued, and she was given 300 mg. daily by the sublingual route for a further 18 days. There was no change in her condition until the 14th day, when she stated that the pains in her feet were much less, but that the ankles were worse. Clinically there appeared to be great pain on movement of the ankles. The range of ankle and knee movements had not altered. On the 40th day, when the pregnenolone administration was stopped, there was no objective change in her condition, although she believed that she had made a general improvement.

Case 7. Male, aged 38 years.—Onset afebrile a year ago with pain in his right ankle.

Soon afterwards the knees, shoulders, hands, elbows, and wrists became swollen and painful. The family history shows nothing of importance except that one sister had an attack of "rheumatism" which quickly disappeared. There is no evidence of peripheral vascular disturbances in the hands or feet.

Examination.—There are fusiform swellings of the 1st, 2nd, and 3rd metacarpo-phalangeal joints of both hands. Both wrists are swollen and painful, while both ankles have a limited range of movement. He has lost weight since the onset of the arthritis and now weighs 9 st. 4 oz. (normal weight 11 st.). No abnormality of the respiratory, cardiovascular, digestive, urinary, or nervous systems was found.

X-Ray Examination.—The left knee shows definite generalized bone rarefaction. Similar changes, but less advanced, are present in the right knee. The distal interphalangeal joints of both hands show early marginal hypertrophic changes and all interphalangeal joint spaces are narrowed. Areas of rarefaction are present in the heads of the 2nd, 3rd, and 4th metacarpal bones of the right hand.

Laboratory Findings.—Serum colloidal gold reaction—positive (2); glucose tolerance test normal; plasma uric acid 4 mg. per 100 ml.

Therapy.—300 mg. pregnenolone were given for 36 days by sublingual route. During the first 17 days the patient experienced considerable pain, worse than before pregnenolone administration, in both feet. On the 18th day the pain abated, but he was conscious of stiffness in the feet and thighs which eased after about 20 minutes exercise. There was no change in body weight. From this time onwards his general health improved, his joint pains lessened and he began to think less of himself and more about his surroundings and the other patients. By the 36th day he had gained 10 lb. in body weight, his joint pains were negligible, and he was able to get about more freely than before pregnenolone administration. Next day he was discharged on a daily maintenance dose of 50 mg. Examination five weeks later showed that he had continued to improve at home and was able to work a full day from 7.30 a.m. to 5.30 p.m. as a foreman plater, without any difficulty. He had some slight pain on pressure over the 4th metacarpo-phalangeal joint of the right hand in addition to tenderness on the plantar surface of his feet. This patient showed a marked clinical improvement during the 36 days he was given pregnenolone, in spite of the increase in plasma viscosity and E.S.R. over the same period.

Case 8. Female, aged 24 years.—Had tonsillitis seven years ago. Four weeks later she experienced pain and stiffness of the fingers, which was most marked in the mornings. The pain spread to the feet, which became swollen. She has had three courses of gold without effect. During the past year the elbow joints and mandibular joints have become involved. In consequence she finds it difficult to feed herself or brush her teeth. Onset of the disease was afebrile, insidious, and polyarticular. There is no family history of rheumatoid arthritis. No signs of peripheral vascular disturbances have been observed beyond frequent attacks of chilblains.

Examination.—Movements of both hands and wrists are limited. There are fusiform swellings of the metacarpo-phalangeal and proximal interphalangeal joints of both hands and wrists. The metatarsal joints of both feet and the right ankle are painful and slightly swollen. There is a complaint of stiffness in the hip joints and the lumbar spine. Her present weight is 8 st. 12 lb. (normal 10 st. 2 lb.). No abnormality was detected in the respiratory, cardiovascular, nervous, digestive, or urinary systems. The blood pressure is low (98/60 mm. Hg).

X-Ray Examination.—Both hands and wrists show widespread joint destruction. The first metatarso-phalangeal joints of both feet are affected, the scaphoid joint and the left shoulders. The left elbow shows evidence of some articular erosion of the sigmoid fossa. The knees, ankles, and spine appear normal. The left shoulder shows osteoporosis and evidence of acromio-clavicular arthritis.

Laboratory Findings.—Serum colloidal gold reaction—negative.

Therapy.—30 mg. pregnenolone were given for eight days intramuscularly. Examination at the end of the period showed no clinical change in her condition. The plasma viscosity and erythrocyte sedimentation rate were substantially unaltered. However,

one year later she had improved to such an extent that she had returned to her work as a typist and could work a full day without any ill effect.

Case 9. Female, aged 24 years.—Rheumatoid arthritis of five years duration. It began with stiffness of the proximal interphalangeal joint of the middle finger of the right hand. The other fingers were soon involved as well as those of the left hand. Six months later the feet were affected and the condition remained static for about two years. At this time she became pregnant and the stiffness and much of the swelling disappeared. Three months after delivery, her condition was as bad as ever. Since then the disease has spread to the wrists, shoulders, and knees, and her general health has deteriorated with loss of weight. She had a course of gold therapy in 1946 followed by a temporary improvement. A second course in 1948 caused a mild dermatitis. There is no family history of rheumatism. The onset of the disease was afebrile, insidious, and polyarticular. No peripheral vascular disturbances have been observed.

Examination.—There are fusiform swellings of the proximal interphalangeal joints and metacarpo-phalangeal joints of both hands and wrists. There are also fusiform swellings of the metatarso-phalangeal joints of both feet. Her present weight is 7 st. 12 lb. (normal 9 st.). Nothing abnormal was found in the respiratory, cardiovascular, nervous, digestive, or urinary systems.

X-Ray Examination.—The hands and wrists show marked narrowing of the articular spaces. There is also narrowing of the spaces in the proximal interphalangeal joints of the left middle finger and the ring finger of the right hand. The other finger joints are affected in a lesser degree. Osteoporosis is generalized, but slight. The appearances of the feet are similar to the hands. There is some bone absorption of the superior surface of the left scaphoid. The knees and ankles are normal.

Laboratory Findings.—Serum colloidal gold reaction—positive (1); plasma uric acid 3·7 mg. per 100 ml.

Therapy.—10 mg. pregnenolone were given intramuscularly for 9 days. There was no change in her clinical condition in response to the injections, nor was there any change in the plasma viscosity, erythrocyte sedimentation rate, or general blood picture.

Case 10. Male, aged 50 years.—In 1941 this patient was on active service with H.M. Forces in Iceland, where he was subject to extremes of climate such as blizzards, gales, and adverse weather conditions. His general health was excellent until he was involved in a motor accident, when a car in which he was travelling fell about 40 ft. over a precipice. He suffered no immediate serious results of the accident. For about 18 months he experienced pain and tenderness in the hands and feet without any swelling. Then the proximal phalangeal joints of both hands became swollen and painful. The onset of the condition was afebrile, insidious, and polyarticular. He has never experienced any peripheral vascular disturbances in the hands, fingers, feet, or toes, and no reaction to a change of locality has been observed. From 1942, when the first signs of rheumatoid arthritis became evident, his condition became slowly, but progressively, worse. Since 1948 the disease has become more acute and painful. There is no history of rheumatism in his family as far back as his maternal and paternal grandparents. In June, 1949, he was admitted to hospital.

Examination.—He is a thin type weighing 9 st. 4 lb. (weight in 1942 10 st. 12 lb.). There are marked rheumatoid deformities with ulnar deviation in both hands. The cardiovascular, nervous, and digestive systems are normal. There was no history of any infections or disturbances of the genito-urinary system. There was marked difficulty in walking on account of tenderness of his feet and muscular pain in the calves and thighs, especially after exercise. Both arms showed wasting of hand, forearm, and arm muscles in addition to a limitation of movements. They were easily fatigued. Movement of the mandibular joints produced pain in the right side.

X-Ray Examination.—The bones of both hands show generalized osteoporosis. There are marked deformities with erosion of bone. The condition of the metacarpo-phalangeal joints and interphalangeal joints could not be determined because of the extensive destruction. The right foot showed arthritis in the first metatarso-phalangeal joint with centres of rarefaction in the region of the second metatarso-phalangeal joint.

Laboratory Findings.—Serum colloidal gold reaction—positive (3); B.M.R. —15 per cent.

Therapy.—This patient was started on 10 mg. pregnenolone intramuscularly for 14 days. As no changes were recorded in his clinical condition or laboratory tests, the daily dose was increased to 60 mg. during the next 7 days—again without result.

Because of the tenderness which had developed at the site of the injections, it was decided to stop all injections for 14 days and then to increase the amount injected to 150 mg. per injection.

During the 14-day rest period, the erythrocyte sedimentation rate rose from 24-22 per cent. to 40-40 per cent. while the plasma viscosity increased from 20·0 to 21·5. Such a marked change was unexpected as well as difficult to explain. These changes were accompanied by an increase in joint pains which became so severe as to interfere with normal sleep.

In spite of this retrogression in his condition, it was decided to continue the administration of pregnenolone without further delay. This was done for 12 days, at the end of which time his condition was re-assessed. The erythrocyte sedimentation rate had risen further from 40-40 per cent. to 45-43 per cent. while the plasma viscosity had increased from 20·0 to 21·5. At this stage it was decided to abandon the intramuscular injections and to give, instead, 300 mg. pregnenolone sublingually for 21 days. This dose was well tolerated. At the end of the period there was no doubt that his arthritis had become distinctly worse. Whilst he was still in good spirits, there was not the slightest doubt that he was worried about his condition. The pain was much more intense, and he confessed that he could only bear it by taking tab. Codeine Co. Both knees were very swollen, tender, and painful. The fingers of both hands were contracted and were extremely painful to touch or to move. The ulnar deviation was marked in spite of the use of splints.

Discussion

This investigation shows that of ten patients treated with pregnenolone, only one (Case 7) showed any marked improvement. In this patient the joint pains became worse during the first 17 days; on the 18th day the pain suddenly abated and the joints remained stiff. By the 36th day the joint pains were negligible, and the patient had gained 10 lb. in body weight. In spite of this diminution in joint pain, the erythrocyte sedimentation rate and plasma viscosity showed increased values over the same period. The patient was able to walk more easily than before, but the entire improvement appeared to be due to the diminution in joint pain.

Case 4 also showed some improvement. Pain in the affected joints was reduced after 7 days' treatment; the patient developed a more cheerful outlook and his hand grip was stronger. No alteration in the range of joint movement was recorded during the trial.

A very doubtful improvement was recorded in Cases 1, 2, and 5. Case 1 showed some improvement in her general condition and gained 4½ lb. in body weight. No clinical changes in her arthritic condition were recorded during the 40 days of pregnenolone administration, but she began to walk slightly better and with less pain three weeks after the administration was terminated. This improvement was maintained for two weeks. No alteration in erythrocyte sedimentation rate, plasma viscosity, or *x*-ray findings were recorded. The sequence of events in Case 2 was similar. No clinical changes were recorded while she was taking pregnenolone. Three weeks later she experienced a diminution in the pain in her hip joints and began to walk more easily. No changes were recorded in the erythrocyte sedimentation rate, plasma viscosity, or *x*-ray findings. Case 5 improved in

general condition and gained 2 st. in body weight while taking pregnenolone. His outlook became more cheerful after the first 7 days and, in this respect, he resembled Case 4. On the 10th day the pain in his feet and knees showed a marked diminution, but the metacarpo-phalangeal joints of both hands became swollen, inflamed, and painful. The hands became steadily worse during the next five days while the pain in the feet and knees diminished to negligible proportions. On the 21st day the condition was reversed, for the feet and knees became acutely painful, while the pain and inflammation in the hands began to subside rapidly. No explanation can be offered for this interesting observation. By the 50th day, 9 days after pregnenolone administration had ceased, all the affected joints were much less painful and swollen, and more comfortable, and the patient stated that he could use his joints a little more freely. No changes in erythrocyte sedimentation rate or plasma viscosity were recorded. The *x*-ray findings were substantially the same.

No changes were recorded in Cases 3, 6, 8, and 9. Case 6 showed no alteration until the 14th day, when her feet became less painful, while her ankles became worse. On the 40th day she believed that she had slightly improved, but the findings did not support this view.

Case 10 showed a marked deterioration during the period of pregnenolone administration. His arthritis became very acute, causing great pain and disability. Joint swelling became marked and joint tenderness increased to an almost unbearable point, while the erythrocyte sedimentation rate and plasma viscosity showed a pronounced increase.

In the only two cases who showed changes which might be regarded as an improvement in their joint condition, this appeared to be due to a diminution in joint pain and not to any constitutional changes in the body as a whole. In no case was there any immediate increase in joint movement or any marked improvement in laboratory findings such as the erythrocyte sedimentation rate, plasma viscosity, packed-cell volume, lymphocyte counts, or haemoglobin.

Three patients showed a substantial increase in body weight during the period of the trial, and two of these exhibited a more cheerful psychological outlook.

None of the female patients experienced any change in the pattern of the menstrual cycle during the period of pregnenolone administration.

As most of the changes seen in these patients were of a subjective type, it is difficult to ascribe any of the results to the administration of pregnenolone. Any, or all, of the changes may have been caused by the normal spontaneous variations frequently seen in untreated cases of rheumatoid arthritis. A larger-scale investigation might yield a more decisive result.

Summary

Ten patients, five male and five female, suffering from rheumatoid arthritis were given pregnenolone over periods varying from 5 to 54 days. The daily dose ranged from 19 to 300 mg. pregnenolone, and both intramuscular and sublingual routes were employed.

One patient showed a definite improvement in functional joint condition, another showed a moderate improvement, and three showed a very doubtful improvement. In four cases no improvement was recorded. One patient showed an acute deterioration of function, during which phase, the erythrocyte sedimentation rate and plasma viscosity were raised.

The two cases showing improvement experienced a diminution in joint pain and the improvement may be ascribed to this cause.

Three patients showed an increase in body weight, and two developed a more cheerful psychological outlook. These improvements were not accompanied by any increase in joint movement or any marked change in the erythrocyte sedimentation rate or plasma viscosity.

The pregnenolone was supplied by Messrs. Ciba, Ltd. I am indebted to Dr. G. Lorriman for his assistance.

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Pregnénolone dans le Traitement de l'Arthrite Rhumatismale

RÉSUMÉ

Dix malades, 5 hommes et 5 femmes, atteints d'arthrite rhumatismale, furent traités par la pregnénolone pendant des périodes de 5 à 54 jours. Ils recevaient, par la voie intramusculaire ou sous-linguale, de 19 à 300 mg. de pregnénolone par jour.

L'amélioration, portant sur la fonction articulaire, fut nette chez un malade, modérée chez un autre et très douteuse chez trois autres. Dans quatre cas on ne constata aucune amélioration. Chez un malade il eut une détérioration aiguë de la fonction, accompagnée de l'élévation de la sédimentation globulaire et de la viscosité plasmatique.

On peut attribuer l'amélioration dans les deux cas favorables à la diminution de la douleur articulaire.

Trois malades ont pris du poids et deux malades ont adopté une meilleure attitude mentale. Cette amélioration n'a pas porté sur l'amplitude du mouvement articulaire, sur la sédimentation globulaire ni sur la viscosité du plasma.

Pregnenolona en el Tratamiento de la Artritis Reumatoide

RESUMEN

Diez enfermos, 5 hombres y 5 mujeres, fueron tratados con pregnenolona durante períodos de 5 a 54 días. La dosis diaria, por vía intramuscular o perlingual, fué de 19 a 300 mg.

La función articular mejoró marcadamente en un enfermo, moderadamente en otro y dudosamente en tres. En cuatro casos no se vió mejoría alguna. En un enfermo hubo deterioración aguda de la función, con elevación de la sedimentación de los eritrocitos y de la viscosidad del plasma.

En los dos casos favorables se puede atribuir la mejoría a la disminución del dolor articular.

Tres enfermos ganaron peso y dos enfermos adoptaron una actitud más optimista. Durante esta mejoría la sedimentación eritrocitaria, la viscosidad del plasma y el movimiento articular no cambiaron.

PLASMA AND SERUM PROTEINS IN CHRONIC RHEUMATIC DISEASES

BY

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From a study of the abnormal serum protein patterns which are characteristic of rheumatoid arthritis, Wallis (1950) has concluded that the hyperglobulinaemia is the result of the combined effects of inflammation, tissue destruction, and immunization, the last being the principal contributor in all but the early stages of the disease. His technique for protein investigations included a preliminary determination of serum albumin/globulin ratios by sodium sulphate fractionation, followed by electrophoretic and immunological studies of the sera from selected patients in whom the A/G ratios had been found to be low.

This work, with previous studies of a similar nature by many other investigators (reviewed by Gutman, 1948), has shown that changes in the serum proteins in rheumatoid arthritis characteristically lead to a decrease in albumin and an increase in globulin. There is also an increase in plasma fibrinogen. The increase in globulin is due chiefly to increments in the alpha- and gamma- fractions, of an extent and proportion referable to the stage of the disease, although the bulk of the increase cannot be accounted for by the development of specific antibodies.

The complex techniques used in these researches are too elaborate for routine use in the clinical laboratory. For simplicity, many workers have adopted indirect methods for assessing protein changes in the plasma or serum of rheumatic patients.

The plasma viscosity test (surveyed by Houston and others, 1949) yields information concerning the plasma proteins by providing an integral measure of their molecular asymmetry. In this respect, the large prolate spheroid molecules of fibrinogen contribute principally, while other asymmetric molecules exert an additional, though smaller, effect. The measurement of serum viscosity does not appear to have been adopted as a clinical test method, except for its use by Lawrence (1949) as part of his elaborate differential plasma viscosity test.

The erythrocyte sedimentation test has been interpreted in terms of plasma proteins through electrophoretic and other investigations. These have been summarized by Gutman (1948) and by Marrack and Hoch (1949) with the conclusion that, in chronic diseases, rapid sedimentation results chiefly from an increase in plasma fibrinogen and a decrease in albumin.

The serum thymol turbidity test, shown by Carter and Maclagan (1946) to be useful in studying rheumatoid arthritis, yields results in this type of disease

which are apparently due to an increase in serum gamma-globulin and a decrease in albumin (Marrack and Hoch, 1949; Marrack and others, 1950).

The thymol turbidity test has been studied in various diseases by Dreyfuss (1948) in parallel with a serum dilution turbidity test, with the conclusion that the two tests yield results which are closely similar and that they probably depend upon similar deviations in serum protein patterns. Both positive thymol turbidity and positive dilution turbidity tests were noted by Dreyfuss in patients with rheumatoid arthritis.

Present Investigations

The aim of the investigations presently described was to demonstrate that quick and simple methods for fractionation and chemical determination of plasma proteins can provide useful information in the routine study of chronic rheumatic conditions. Since an increment in the globulin moiety appears to be the most dependable feature of the altered protein patterns found in such conditions, this fraction was chosen as a basis for the grouping of the analytical results. The indirect tests mentioned above were also adopted in the investigations with the purpose of assessing their value as indicators of protein abnormalities.

Analytical data were recorded in three groups for blood samples from 152 patients whose conditions included sub-acute (active) and chronic (inactive) rheumatoid arthritis, osteo-arthritis, and fibrositis.

Analytical Methods

The estimations of plasma total protein, of plasma globulin (including fibrinogen), and of serum globulin, recorded in Table I, were made by the direct dispersimetric method of Salt (1950), in which the globulin is fractionated by methanol. Albumin values were obtained by difference between total protein and globulin.

In subsequent analyses (Tables II and III), the serum protein fractions were separated by means of sodium sulphite at concentrations of 15·0, 18·0 and 21·0 per cent., as described by Campbell and Hanna (1937). The protein concentrations in the sulphite filtrates and the total protein concentrations of saline-diluted sera were then each determined by an adaptation of the biuret reaction of Sunderman and Schmidt (1944), followed by absorptiometric measurements in the photelometer described by Salt (1950), with narrow waveband yellow-green light (Ilford filter No. 605). Using these procedures, accurate determinations were quickly completed and the various protein fractions were computed by differences.

Fibrinogen concentrations were estimated directly by micro-Kjeldahl digestion of the protein precipitated from plasma by 12·5 per cent. sodium sulphite (Campbell and Hanna, 1937), followed by nesslerization and absorptiometry, using spectral blue light (Ilford filter No. 602). All values for total protein and for protein fractions are given in g. per 100 ml. serum or plasma.

Erythrocyte sedimentation tests were performed by the method of Collins and others (1939), and values were recorded as clear plasma per cent. by volume at one hour. The values were then adjusted to corrected sedimentation rates on the basis of erythrocyte packed-cell volume. Further details have been given by Arnold and Salt (1950), together with an estimate of the degree of correlation which exists between corrected sedimentation rate and plasma viscosity values.

Plasma or serum viscosity values were determined by the technique described by Woodmansey and Wilson (1948) and recorded in millipoise units. The technique is

simple and is characterized by about the same degree of accuracy as the corrected sedimentation rate test (Dawson and Salt, 1950).

The thymol turbidity tests were carried out by the technique of Maclagan (1944), except that volumes of serum and reagent were doubled, and the dilution turbidity tests by the method of Dreyfuss (1948). The results in each case were determined by light-dispersion measurements in the photelometer (Salt, 1950) with spectral red light (Ilford filter No. 608), using standards prepared from known amounts of serum protein precipitated with salicylsulphonic acid. The results for each of the turbidity tests are recorded in Maclagan's arbitrary units.

Results

Table I presents a summary of the analytical results derived from the blood samples of 38 unselected patients, sixteen of whom yielded values for plasma globulin (including fibrinogen) of less than 3·0 per cent., and 22 values greater than 3·0 per cent. Mean values with standard deviations are shown for each sub-group, together with the values for t and P (Fisher, 1941) which furnish a statistical evaluation of the magnitude and significance of the differences between the means.

TABLE I

SUMMARY OF ANALYTICAL DATA FROM BLOOD SAMPLES OF 38 PATIENTS*

Proteins	Plasma Globulin (including Fibrinogen)								Statistical Evaluation of the Difference between the Means	
	Below 3·0 per cent. (16 patients)				Above 3·0 per cent. (22 patients)					
	Range of values found	Mean value	S.D.	Mean ± 2S.D.	Range of values found	Mean value	S.D.	Mean ± 2S.D.	t	P
Plasma (oxalated)										
Globulin (inc. fibrinogen) ..	2·4 - 2·95	2·73	0·17	2·39- 3·07	3·00- 3·96	3·31	0·27	2·77- 3·85	7·67	<0·001
Viscosity ..	16·2 -21·3	18·6	1·36	15·9 -21·3	18·5 -25·6	20·8	1·88	17·0 -24·6	3·96	<0·001
Corrected sedimentation rate	10·0 -34·0	20·0	7·04	6·0 -34·0	11·0 -44·0	31·0	10·1	11·0 -51·0	3·74	0·001
Albumin ..	4·08- 5·46	4·97	0·34	4·29- 5·65	3·58- 5·46	4·55	0·42	3·71- 5·39	3·27	0·001
Fibrinogen ..	0·24- 0·43	0·31	0·05	0·21- 0·41	0·26- 0·52	0·37	0·08	0·21- 0·53	2·61	0·01
Total protein ..	6·78- 8·41	7·7	0·34	7·02- 8·38	7·08- 8·92	7·87	0·42	7·03- 8·71	1·33	0·2
Serum										
Globulin ..	1·82- 3·48	2·54	0·28	1·98- 3·1	2·44- 3·8	2·84	0·35	2·14- 3·54	2·85	0·01
Viscosity ..	13·7 -19·5	16·5	1·33	13·8 -19·2	15·3 -21·1	17·7	1·29	15·1 -20·3	2·80	0·01

* Units of measurement given in text under " Analytical Methods ".

The differences in plasma globulin (including fibrinogen) concentrations determined chemically, are seen to be closely paralleled by the values for plasma viscosity and for corrected sedimentation rate. A significant diminution in the albumin content of the plasma also accompanies the augmented globulin and fibrinogen levels, whereas the fibrinogen content differs only slightly in the two sub-groups. The mean values for plasma total protein concentrations do not differ significantly (P is greater than 0·05), probably because the series did not happen to include many of the more grossly abnormal plasmas. Significant differences for serum globulin concentrations and for serum viscosity values suggested the possibility that detailed analysis of serum might yield results of greater value than the analyses of plasma.

TABLE II

SUMMARY OF ANALYTICAL DATA FROM BLOOD SAMPLES OF 61 PATIENTS*

Proteins	Serum Globulin								Statistical Evaluation of the Difference between the Means	
	Below 3·0 per cent. (25 patients)				Above 3·0 per cent. (36 patients)					
	Range of values found	Mean value	S.D.	Mean ± 2S.D.	Range of values found	Mean value	S.D.	Mean ± 2S.D.	*t*	*P*
Serum										
Globulin ..	1·91- 2·95	2·48	0·3	1·88- 3·08	3·04- 5·18	3·7	0·58	2·54- 4·86	9·6	<0·001
Total protein ..	6·53- 8·92	7·67	0·61	6·45- 8·89	7·19- 9·73	8·57	0·62	7·33- 9·81	5·61	<0·001
Euglobulin ..	0·6 - 1·98	1·27	0·34	0·59- 1·95	0·94- 3·46	1·97	0·65	0·67- 3·27	4·98	<0·001
Pseudoglobulin I	0·15- 0·96	0·63	0·25	0·13- 1·13	0·31- 1·66	1·0	0·32	0·36- 1·64	4·9	<0·001
Pseudoglobulin II	0·19- 0·97	0·58	0·21	0·16- 1·0	0·22- 1·38	0·74	0·31	0·12- 1·36	2·28	0·02
Albumin ..	3·74- 6·53	5·19	0·68	3·83- 6·55	3·74- 6·2	4·87	0·37	4·13- 5·61	2·12	0·05
Plasma (oxalated)										
Corrected sedimentation rate	0·0 -47·0	23·0	14·7	(6)†-52·0	7·0 -47·0	37·0	10·57	16·0 -58·0	4·32	<0·001
Fibrinogen ..	0·24- 0·8	0·41	0·13	0·15- 0·67	0·18- 0·96	0·51	0·16	0·19- 0·83	2·56	0·01

* Units of measurement given in text under " Analytical Methods ".
† Indicates a minus value.

Table II contains a summary of the analytical results derived from the blood samples of a further 61 patients, 25 of whom yielded values for serum globulin of less than 3·0 per cent. and 36 values greater than 3·0 per cent.

Differences in the serum globulin concentrations are evident also in the values for serum total protein; and of the globulin fractions, increments in the euglobulin and pseudoglobulin I components are those which contribute principally to globulin increases. Serum albumin shows a small (just significant) difference, opposite in direction to the globulin differences. The corrected sedimentation rate values, which may be held to indicate abnormalities of plasma protein structure, also show differences in this series corresponding to the differences in serum globulins, whereas the plasma fibrinogen concentrations show only slight differences.

TABLE III

SUMMARY OF ANALYTICAL DATA FROM BLOOD SAMPLES OF 53 PATIENTS*

Proteins	Serum Globulin								Statistical Evaluation of the Difference between the Means	
	Below 3·0 per cent. (27 patients)				Above 3·0 per cent. (26 patients)					
	Range of values found	Mean value	S.D.	Mean ± 2S.D.	Range of values found	Mean value	S.D.	Mean ± 2S.D.	*t*	*P*
Serum										
Globulin ..	1·98- 2·98	2·62	0·28	2·06- 3·18	3·01- 4·18	3·5	0·35	2·8 - 4·2	10·33	<0·001
Euglobulin ..	0·69- 1·88	1·33	0·33	0·67- 1·99	1·19- 2·61	1·88	0·37	1·14- 2·62	5·72	<0·001
Total protein ..	6·97- 8·41	7·66	0·38	6·9 - 8·42	7·44- 9·73	8·34	0·52	7·3 - 9·38	5·38	<0·001
Viscosity ..	15·3 -20·3	17·2	1·17	14·9 -19·5	16·4 -21·8	18·6	1·36	15·9 -21·3	4·04	<0·001
Thymol turbidity test ..	1·0 - 6·0	2·9	1·31	0·3 - 5·5	1·0 - 8·5	4·3	2·08	0·1 - 8·5	2·95	0·01
Dilution turbidity test ..	1·0 - 4·0	2·3	0·84	0·6 - 4·0	1·0 - 5·0	3·0	1·1	0·8 - 5·2	2·6	0·01
Plasma (oxalated)										
Viscosity ..	18·1 -24·1	19·7	1·41	16·9 -22·5	18·6 -28·4	22·1	2·26	17·6 -26·6	4·65	<0·001
Corrected sedimentation rate	11·0 -45·0	28·0	10·42	7·0 -49·0	4·0 -46·0	32·0	13·22	6·0 -58·0	1·24	0·2

* Units of measurement given in text under " Analytical Methods ".

A third series of analytical results is summarized in Table III. These were

derived from the blood samples of a further 53 patients, who were sub-divided in the same way as the previous series, 27 patients having serum globulin levels below 3·0 per cent., and 26 patients levels above 3·0 per cent. The analytical methods chosen for this series included three indirect serum protein tests and two indirect plasma protein tests, as well as estimations of serum euglobulin and total protein concentrations.

The differences in the sub-groups based on serum globulin concentrations are demonstrated also by the euglobulin and total protein values in a manner very similar to that seen in the previous experiments of Table II, and the serum viscosity values likewise afford a similar means of differentiation. The significance of the plasma viscosity values appears to correspond closely to that of the serum viscosity values, but in this series the corrected sedimentation rates do not differ significantly in the two sub-groups (P is less than 0·05). The thymol turbidity and dilution turbidity tests appear to be of only moderate value as indicators of hyperglobulinaemia.

In order to compare the value of the different tests, the data summarized in Table III were re-arranged in five groups, based on ranges of serum globulin concentration, and mean values were calculated for each group (Table IV). It is evident that each type of analysis shows the same general trend of values corresponding with the gradation of serum globulin, but that the tests vary in their degree of correspondence. As indicators of hyperglobulinaemia, the thymol turbidity and dilution turbidity tests appear to be less sensitive than the serum viscosity or plasma viscosity values, and the corrected sedimentation rate (in this series) is the least sensitive of the tests.

TABLE IV

ANALYTICAL VALUES FROM 53 PATIENTS, BY SERUM GLOBULIN*

No. of Analyses	Range of Serum Globulin Concentration	Mean Values of Corresponding Analyses						
		Serum					Plasma	
		Euglobulin	Total protein	Viscosity	Thymol turbidity test	Dilution turbidity test	Viscosity	Corrected sedimentation rate
9	2·0-2·5	1·1	7·54	16·7	2·7	2·1	19·2	26
18	2·5-3·0	1·45	7·71	17·5	3·0	2·7	19·9	28
14	3·0-3·5	1·7	8·13	18·1	3·7	2·7	21·4	29
9	3·5-4·0	2·0	8·41	19·1	4·4	3·2	22·4	32
3	4·0-4·5	2·35	9·11	19·2	6·2	3·8	24·2	44

* Units of measurement given in text under " Analytical Methods ".

Conclusions

As a general conclusion from the experiments, it appears evident that the hyperglobulinaemia demonstrable in patients with chronic rheumatic disease is due chiefly to increments in the euglobulin and pseudoglobulin I fractions, which can be evaluated by simple chemical analysis. Serum total protein concentrations may also be increased because of the hyperglobulinaemia, but the increment may be partially off-set by a depletion in the albumin component. Variations in plasma fibrinogen concentration do not necessarily parallel those in serum globulin,

so that the estimation of fibrinogen and the measurement of plasma viscosity or corrected sedimentation rate, which appear to depend principally on fibrinogen, yield results only approximately related to the hyperglobulinaemia. Measurements of serum viscosity seem to merit further study, although the non-specific nature of this type of test suggests that direct determinations of serum globulin or euglobulin are to be preferred. The methods which have been used in the present experiments are recommended for ease and precision; further work is in progress with the purpose of improving them yet further. It should be noted that the protein fractions, apart from plasma fibrinogen, are determined most successfully by the use of samples of serum.

Discussion

The abnormalities of individual protein fractions and the changes in the results of empirical tests are alike unrelated specifically to chronic rheumatic disease. The use of empirical tests has developed after the classical precedent of the determination of erythrocyte sedimentation rate, and many such tests are now in use. Often these have the advantages of speed, simplicity, and clinical signification, but they vary in sensitivity and in their applicability to different problems arising in the laboratory study of diseases. In chronic rheumatic diseases, Carter and Maclagan (1946) found the serum colloidal gold test to be more sensitive than the thymol turbidity test. Fraser (1948) further studied the colloidal gold test and found the cephalin-cholesterol flocculation test of little value in rheumatoid arthritis. In the present studies, the thymol turbidity test was adopted because the turbidity measured is largely due to precipitated gamma-globulin; and the dilution turbidity test was chosen because it forms a measure of serum beta-lipoprotein and gamma-globulin.

Lawrence (1949) has developed an elaborate differential plasma viscosity test for the purpose of delineating plasma protein patterns. Although this appears to be superior to simple determinations of plasma or serum viscosity, it would seem more appropriate to adopt methods involving separation and direct estimation of the plasma protein components. Mester (1945) has advocated the determination of plasma fibrinogen in addition to the sedimentation rate, and Davis (1936) has made detailed analyses of the plasma protein fractions in arthritis, with results very similar to those of the present experiments. As the analytical methods now available are comparably precise but much less laborious than those used by Davis, and since the various empirical tests have largely been interpreted in terms of protein changes, the direct determinations of protein fractions which could replace the empirical tests with advantage, are to be recommended.

Summary

(1) Changes in the pattern of plasma and serum proteins which may develop in chronic rheumatic conditions and their delineation by various direct methods and by certain indirect empirical tests are considered. It is recognized that none of these changes is specifically related to rheumatic disease.

(2) A summary of the analytical data recorded for blood samples from 152 patients is presented in four Tables, together with statistical evaluations. The data include values for plasma or serum total protein, total globulin fractionated by methanol, euglobulin and pseudoglobulins I and II fractionated by different concentrations of sodium sulphite, albumin, and fibrinogen, together with corrected sedimentation rates, viscosity measurements, and the results of thymol turbidity and dilution turbidity tests. The grouped data are classified according to the presence or absence of hyperglobulinaemia.

(3) It is shown that hyperglobulinaemia is chiefly due to increments in the euglobulin and pseudoglobulin I fractions. These increments can be demonstrated readily by precise but simple chemical determinations.

(4) Various empirical tests which have been advocated for the laboratory study of chronic rheumatism are discussed. Such tests vary in sensitivity and in the nature of the plasma or serum abnormalities indicated. It is concluded that empirical tests could be replaced with advantage by direct determinations of plasma or serum protein components.

I wish to thank Dr. H. L. Milles and Dr. J. E. Dawson for their co-operation in providing access to their patients; and Miss P. Arnold for performing many of the analyses.

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Protéines du Plasma et du Sérum dans les Maladies Rhumatismales Chroniques

Résumé

(1) L'auteur étudie les modifications du taux des protéines du plasma et du sérum survenant au cours des maladies rhumatismales chroniques ainsi que les méthodes directes et indirectes ou empiriques par lesquelles ce taux est déterminé. Il est entendu qu'aucune de ces modifications ne se rapporte spécifiquement à la maladie rhumatismale.

(2) Quatre tableaux présentent un résumé des données de l'examen du sang de 152 malades, ainsi que l'évaluation statistique de ces données. Ces déterminations quantitatives portent sur: protéines totales du plasma et du sérum, globuline totale fraccionnée au méthanol, euglobuline et pseudoglobuline I et II fraccionnées en concentrations différentes de sulfite de soude, albumine,

fibrinogène, sédimentation globulaire corrigée, turbidité au thymol et turbidité en dilution. Dans chaque tableau le groupement des résultats est déterminé par la présence ou par l'absence de l'hyperglobulinémie.

(3) L'hyperglobulinémie est due surtout à l'augmentation du taux de l'euglobuline et de la pseudoglobuline I. Cette augmentation peut être démontrée facilement par des analyses chimiques simples mais précises.

(4) L'auteur discute les différentes méthodes empiriques recommandées pour l'étude de laboratoire du rhumatisme chronique. La sensibilité de ces méthodes est variable et les résultats n'indiquent pas la nature des anomalies des protéines sanguines. L'auteur conclut qu'il y aurait avantage à remplacer les méthodes empiriques par des analyses directes des protéines du plasma et du sérum.

Proteinas del Plasma y del Suero en las Enfermedades Reumàticas Crónicas

RESUMEN

(1) El autor estudia las alteraciones de los valores de las proteinas del plasma y del suero en el curso de las enfermedades reumáticas crónicas así como los méthodos, directos e indirectos o empíricos, de determinación de estos valores. Reconoce que estas alteraciones no tienen carácter específico en la enfermedad reumática.

(2) Cuatro cuadros presentan el resumen de los datos obtenidos al analizar la sangre de 152 enfermos, así como la valuación estadística de estos datos. Se determinaron: proteinas totales del plasma y del suero, globulina total fraccionada por metanol, euglobulina y pseudoglobulina I y II fraccionadas por varias concentraciones de sulfito de sodio, albumina, fibrinogeno, sedimentación globular corregida, turbiedad al timol y turbiedad en dilución. En los cuadros la agrupación de los resultados fué determinada por la existencia o la ausencia de la hiperglobulinemia.

(3) La hiperglobulinemia se debe principalmente al aumento de la euglobulina y de la pseudoglobulina I. Este aumento se puede demostrar fácilmente por análisis químicos simples, pero precisos.

(4) El autor discute los varios métodos empíricos propugnados para el estudio de laboratorio del reumatismo crónico. La sensibilidad de estos métodos es variable y sus resultados no indican la naturaleza de las abnormalidades de las proteinas sanguineas. Conclude que habría ventaja en sustituir los métodos empíricos por análisis directos de las proteinas del plasma y del suero.

PREGNANCY IN ANKYLOSING SPONDYLITIS

A REPORT OF TWO CASES

BY

F. DUDLEY HART, A. C. H. BELL, and G. S. W. ORGANE

From the Westminster Hospital, London

Ankylosing spondylitis is relatively uncommon in females, the sex ratio usually lying in the region of 10 : 1, male : female. The question of pregnancy occurring in spondylitics, however, still arises as, compared with rheumatoid arthritis, the age at onset is considerably less, spondylitis usually starting in the third decade. In view of the early fixation of sacro-iliac joints and the general pelvic rigidity in advanced cases, the management of such a patient demands close co-ordination between physician, obstetrician, and anaesthetist. References to pregnancy in spondylitis are not common; Steinberg (1948) gives case histories of three patients, only one of whom was observed throughout pregnancy by the author. In view of the not uncommon dramatic reversal of the clinical picture in rheumatoid arthritis when pregnancy occurs, the two following case histories are of interest, for such improvement failed to occur in either subject.

Case Histories

Case 1. Married Woman, aged 31. Pain in the right hip on walking commenced in 1939. This was intermittent and disappeared completely in 1946. In 1943 pains across the back were attributed to fibrositis. In 1944 pains commenced in the shoulder girdle, accompanied by a feeling of stiffness. In 1947 an acute bout of pain and stiffness in the neck lasted for two weeks. During this year the pains in the back increased, being worse in the early morning when she felt very stiff. In 1948 the back pain was aggravated by coughing and sneezing, and the front of her chest was also painful. Neck pains returned. *X* rays of the neck were taken and were negative. Previous history and family history were irrelevant.

When first seen by one of us (F.D.H.) in July, 1948, the main complaint was of low backache and stiffness, worse in the morning and improving through the day. Her ribs ached on occasion. On examination physical signs were not marked. The spine appeared to move almost normally. In view of her history skiagrams were taken. These showed ankylosing spondylitis with advanced changes in both sacro-iliac joints, the left being completely ankylosed, the right partially. The intervertebral joints in the lumbar region did not appear to be involved. There was no ligamentous ossification. Hips and ischial tuberosities were normal, and a skiagram of the heart and lungs was also normal.

She was admitted to Westminster Hospital in September, 1948. The only positive findings on examination were restriction of chest expansion below the breasts to $\frac{3}{4}$ inch, slight limitation of movements of the neck and lumbar spine, and some tenderness over the left side of the sternum.

Laboratory Findings :

Sedimentation rate 8 mm. in one hour (Wintrobe) ; three weeks later 24 mm. in one hour.
Wassermann reaction, Kahn test, and gonococcal complement-fixation test negative.
Vital capacity 2,793 ml. (84 per cent. of normal).
Blood count, serum uric acid and urea, thymol turbidity and flocculation tests, and serum colloidal gold reaction all normal.

Deep *x*-ray therapy (Westinghouse) was given to cervico-dorsal and dorsi-lumbar regions by Dr. F. M. Allchin. No sacral port was used to avoid damage to the ovaries.

Dorsi-cervical one direct 15 × 10 cm. port. 1,200r skin.
Lumbo-dorsal one direct 23 × 10 cm. port. 1,200r skin.
Sternum one direct 15 × 10 cm. port. 900r skin.
Factors 200 K.V. 50 cm. F.S.D. 1·6 cu. H.V.L.

Breathing and postural exercises were given in addition.

Before discharge on November 3, 1948, chest expansion had increased to 2¼ inches, and back pain had diminished and mobility increased. Sternal tenderness disappeared completely. Sacral pain (an area not treated) had, however, increased.

On December 1, 1948, she was seen in the Rheumatism clinic. Her neck pains were now slight and gave her no trouble. Her chest felt free and there were no pains on coughing or sneezing. Aches and stiffness persisted in the untreated lumbo-sacral area. Chest expansion had risen to 3 inches. She was now tender over the left iliac crest. On January 26, 1949, sedimentation rate was normal.

Pregnancy.—The patient had been attending a fertility clinic as she and her husband were desirous of producing a family, but over a period of 5 years conception had not occurred. On attendance in September, 1949, she was found to be 4 months pregnant. Aching had recurred down the thoracic spine and tenderness was present over sacro-iliac joints, iliac crests (left more than right), and ischial tuberosities. *X* rays showed changes in both iliac crests, left more than right. The backache abated within three weeks, but bony tenderness in the above sites, worst in the left iliac crest, continued unabated throughout pregnancy. According to the patient, the back " seized up " on one occasion for a week when she was six and a half months pregnant.

Ante-natal progress was normal, the blood pressure never rose above 120/80 mm. Hg, and the urine contained no abnormal constituents.

Blood Test Results :

Wassermann reaction and Kahn test negative.
Blood group O (IV) Rh-positive.
Hb 81 per cent.

On February 2 1950, she was approximately 38 weeks pregnant, the presentation being a vertex left occipito-anterior with the foetal head deeply engaged in the pelvis.

Normal delivery was anticipated and labour commenced on February 15. The first stage lasted only 8 hours 10 minutes, spontaneous delivery of a live male child (6 lb. 15 oz.) taking place after 65 minutes in the second stage. The total duration of labour was 9 hours 55 minutes. The puerperium was quite uneventful and the child was breast fed.

Since pregnancy, bony tenderness continues. During pregnancy there was no alleviation of her symptoms and bony tenderness became more marked. Chest expansion two months after childbirth was reduced to 1¼ inches, and spinal flexion, registered photographically, was reduced to half what it had been before conception. *X* rays showed no appreciable changes in sacro-iliac joints and pelvis, but calcification had occurred in the soft tissues in the lateral aspect between L. 3 and 4.

Comment on Case 1.—Conception, attempted over a period of five years, occurred during a period of increased well-being and freedom from symptoms

following deep *x*-ray therapy to cervico-dorsal and lumbo-dorsal ports, the lower lumbar and sacral areas being untreated. Pregnancy had no alleviating effect; fresh symptoms and physical and radiological signs occurred during pregnancy. Childbirth was uncomplicated and uneventful.

Case 2. Married woman, aged 29. Backache was first noted in 1942 while serving in the A.T.S. at the age of 21. This was constant, but became worse after immobility ;

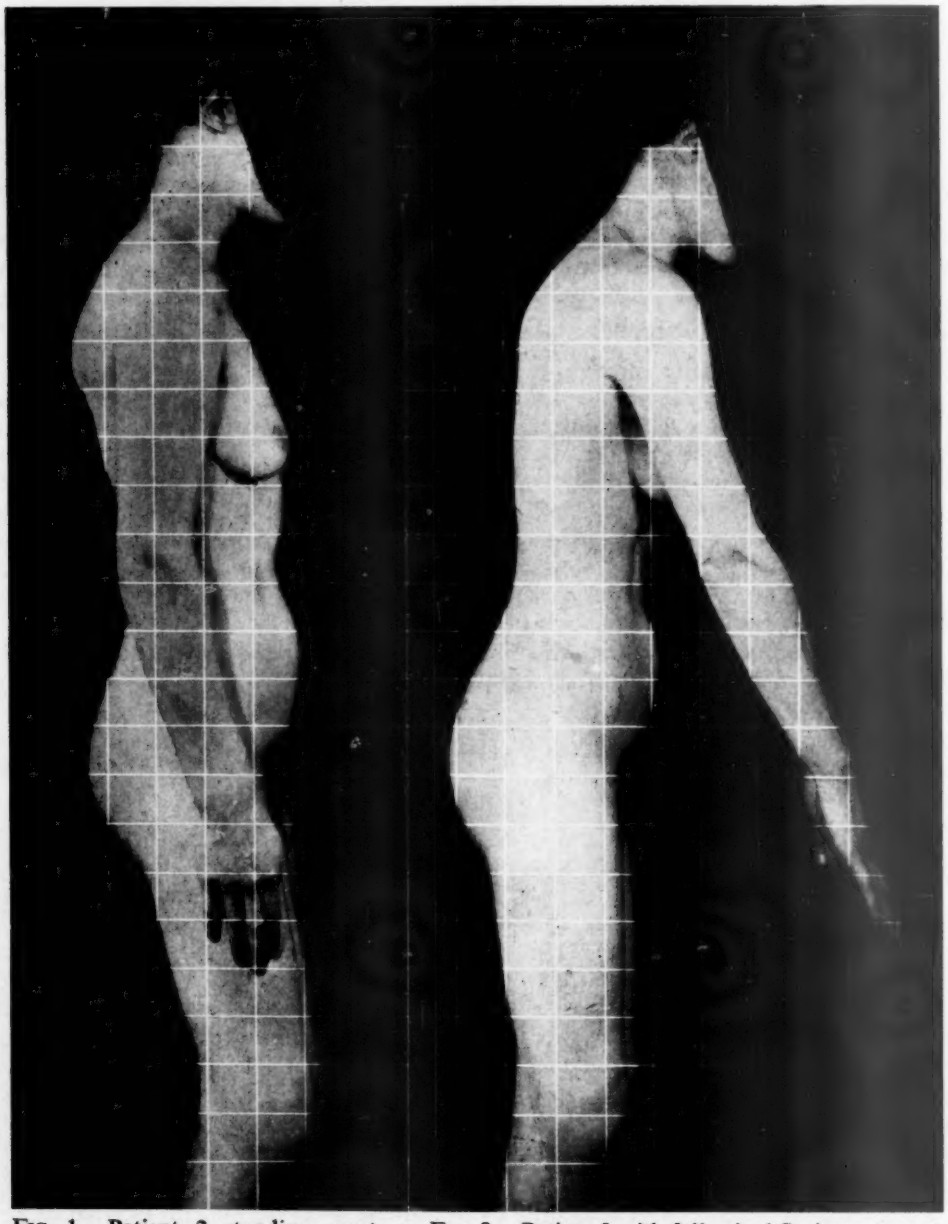

FIG. 1.—Patient 2 standing erect, July, 1948.

FIG. 2.—Patient 2 with full spinal flexion, attempting to touch her toes, July, 1948.

her worst time was on rising in the morning. Skiagrams taken showed changes in sacro-iliac joints and calcification of spinal ligaments. In the following four months pain extended up the spine and stiffness increased ; breathlessness was first noticed on exertion. Early in 1943 a plaster jacket was applied and this was changed subsequently for a plaster bed. She was discharged from the A.T.S. and remained in her plaster bed until April, 1944. She emerged with a completely stiff " poker back ", and her hips also fused. In October, 1945, her neck became stiff and deep *x*-ray therapy was given. Early in 1946 she married. About Christmas, 1947, the temporo-mandibular joints became affected. In June, 1948, both knees became painful and swollen. The previous personal and family histories were entirely negative.

She was admitted to hospital under our care in July, 1948. On examination she was a cheerful, optimistic subject. Chest expansion below the breasts was only $\frac{1}{2}$ inch. Breathing was almost entirely diaphragmatic. The spine was throughout entirely fused with flattening of the lumbar region; no movements of any sort were possible (see Figs 1 and 2). Jaws opened 1 inch. Hips were entirely rigid, fixed in slight flexion. Knee movements were restricted by 50 per cent.—complete flexion and extension being impossible. Ankle, elbow, wrist, and hand movements were all normal. Shoulders retained 75 per cent. of full range. Other systems were normal. She moved about briskly on crutches and was just able to shuffle short distances without them.

Radiographs.—Skiagrams of her entire skeleton showed complete fusion of hips, sacro-iliac joints, all intervertebral articulations, and all costo-transverse and costo-vertebral joints. Calcification of longitudinal ligaments was extensive (Fig. 3). She was a human ramrod, with movement only of her extremities.

FIG. 3.—Radiograph of pelvis of Patient 2, July, 1948. Complete fusion of the hips with no movement at all under anaesthesia. Complete fusion of sacro-iliac joints. Changes present in the symphysis pubis. Longitudinal ligamentous calcification.

Laboratory Findings :

Blood count, Hb 69 per cent. (Haldane);
R.B.C. 4,350,000 per c.mm.;
Colour Index 0·8;
W.B.C. 9,700 per c.mm. with normal differential.
Sedimentation rate 30 mm. in one hour (corrected Wintrobe).
Wassermann reaction, Kahn test, and gonococcal complement-fixation test negative.
Thymol turbidity 1 unit.
Thymol flocculation negative.
Serum colloidal gold reaction 2+.
Vital capacity 2,030 ml. (61 per cent. of normal).

She was discharged and kept under out-patient observation. A woman of high morale, she did not allow her disability to restrict her activities and attended the cinema and theatre taking with her her own home-made portable chair, for she was unable to flex her thighs to sit on the ordinary sort.

Pregnancy.—She was very anxious to have a family, and as early as October, 1947, had consulted one of us (A.C.H.B.) who did not consider it likely she would become pregnant, but thought a Caesarean section would have to be done if conception occurred. At this time ankles could only be separated 3 inches. The uterus was small and retroverted. Investigation of infertility was not considered desirable, even if possible.

On November 9, 1949, she attended the Rheumatism clinic and was found to be ten weeks pregnant.

Laboratory Findings :

Sedimentation rate 31 mm. in one hour (corrected Wintrobe).
Vital capacity 2,100 ml. (69 per cent. of normal).
Hb 70 per cent. (Haldane).
Plasma proteins 7·35 g. per cent. (albumin 4·17 g., globulin 2·60 g., fibrinogen 0·55 g.).
Thymol turbidity test 1 unit.
Thymol flocculation test negative.
Serum colloidal gold reaction 1+.

Examination at the first visit to the Ante-natal clinic showed the hips to be fixed in adduction and slight flexion, no abduction being possible. At this time the patient was ten weeks pregnant. She stated that this followed normal intercourse, although in view of her deformity this had seemed impossible. Her blood pressure was 130/80 mm. Hg, the highest recording at any time during her pregnancy. The urine remained free from albumin and sugar throughout pregnancy.

Blood Test Results :

Wassermann reaction and Kahn test negative.
Blood group A (II) Rh-positive.
Hb 70 per cent.

On December 12, 1949, her condition was unchanged. The vital capacity had increased to 74 per cent.; there was no complaint of dyspnoea; her only complaint being of nausea, and occasional evening vomiting. On January 20, 1950, the vital capacity was 70 per cent. About this time she first noticed œdema of both legs up to the knee (this was slightly worse towards the end of the day, but also still present in the morning to quite a marked degree), and also a new symptom, aching in her right elbow. Two bouts of severe backache, possibly related to long periods of standing, were noted for a few days in the left sacro-iliac and mid-lumbar areas for a few days.

In April, 1950, she exhibited gross oedema of the legs, but no other evidence of toxaemia. The haemoglobin was now 53 per cent. She was admitted for rest and treatment for anaemia, two pints of blood (packed red cells) being given intravenously on April 29. On May 8, the haemoglobin had risen to 86 per cent., and the oedema was considerably less. By this time she was 36 weeks pregnant, the presentation being a

vertex left occipito-anterior. Her general condition was good. It was decided to deliver her at the 36th week by Caesarean section, because delivery *per vias naturales* appeared impossible and respiratory embarrassment was likely owing to fixity of the thoracic cage and the size of the pregnant uterus. The following day a lower segment Caesarean section was performed under general anaesthesia (see note below), and a live female child (5 lb. 11 oz.) was delivered.

The post-operative course was uneventful, normal involution taking place. The patient was semi-ambulant (a special chair being employed) from the second post-operative day in order to forestall any chest complications. The child made good progress and was breast fed. The patient was discharged on May 27, the 19th post-operative day. Subsequent progress was satisfactory. Oedema of the ankles gradually diminished. Intermittent aches in the right elbow and tenderness over the right olecranon wore off after two months. Joints were exactly as before conception and have remained so since. The daily aspirin ration remains constant at two.

Anaesthesia.—The patient was premedicated with atropine gr. 1/100 ; anaesthesia was induced with 0·2 g. thiopentone, and continued in a light plane with nitrous oxide—oxygen and a trace of ether. When she was already unconscious it was realized for the first time that her head was fixed on the neck in a fair degree of flexion, this led to considerable difficulty in maintaining an adequate airway; she was partly obstructed throughout, and there was some cyanosis at times. She recovered very rapidly from the anaesthetic, and there were no difficulties in the post-operative period. The child's movements were not very active, but it cried spontaneously.

In retrospect, it is clear that some form of local, regional, or nerve block would have been the most satisfactory solution. This would have taken the form of a bilateral posterior intercostal nerve block of the 9th, 10th, 11th, and 12th thoracic nerves, with some local infiltration at the lower end of the incision and behind the pubis.

Comment on Case 2.—One of the worst spondylitics attending the Rheumatism Clinic, this girl with rigid thorax and completely fused hips, pelvis, and entire spine, passed through her 36-week pregnancy with no significant reduction in her vital capacity readings (indeed, they appeared to improve slightly) and no complaint of dyspnoea except when lying with head flat or depressed. No improvement or deterioration was noted in her condition and sedimentation rates remained elevated throughout.

Discussion

In two of the cases quoted by Steinberg (1948) there was indication that pregnancy seemed to benefit the spinal condition, though in his Case 2 symptoms had first appeared during pregnancy. This improvement was not noted in our two cases, where remission, often so dramatic in rheumatoid arthritis in pregnancy, failed to appear. In one case there was progression of the disease clinically and radiologically, during pregnancy. Childbirth in this case was entirely normal as in Steinberg's Case 1. Our Case 2, one of the most severe attending the Rheumatism clinic, suffered none of the respiratory embarrassment that we anticipated, her vital capacity increasing slightly during pregnancy. There was no improvement in her condition in any other respect, but neither was there evidence of deterioration.

Summary

The management of pregnancy in two patients with ankylosing spondylitis is described and discussed. One mild case had an easy labour, but her disease appeared to progress during cyesis. The other, a severely ankylosed patient, was delivered of a normal child by Caesarean section in the 36th week. Her vital capacity rose slightly during pregnancy, and although her thorax was completely fused, no respiratory distress was experienced. In neither case was there any symptomatic improvement or sign of true remission during the months of pregnancy.

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Grossesse dans la Spondylite Anquilosante
Rapport de Deux Cas

RÉSUMÉ

Les auteurs décrivent et discutent le maniement de la grossesse chez deux femmes atteintes de spondylite ankylosante. Chez une d'elles le travail se déroula facilement, mais pendant la grossesse la maladie semblait avancer. Chez l'autre femme l'ankylose était grave ; au bout de la trente-sixième semaine on fit l'opération césarienne et un enfant normal naquit. Pendant la grossesse, malgré la fusion complète de son thorax, on n'observa pas de détresse respiratoire et la capacité vitale s'était même élevée un peu. Dans les deux cas pendant toute la durée de grossesse il n'y eut pas d'amélioration objective ni subjective.

El Embarazo en la Espondilitis Anquilosante
Relato de Dos Casos

RESUMEN

Los autores describen y discuten el manejo del embarazo en dos mujeres con espondilitis anquilosante. En una de ellas la labor fué fácil pero durante el embarazo la enfermedad parecía progresar. En la otra mujer la anquilosis era grave ; al cabo de treinta y seis semanas un niño normal fué extraido por operación cesárea. Durante el embarazo, a pesar de la fusión completa del tórax, no se vió angustia respiratoria, y la capacidad vital estaba algo aumentada. En ambos casos durante el embarazo no hubo mejoría objetiva ni subjetiva.

SPONDYLITIS FOLLOWING WEIL'S DISEASE

BY

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Cases of infective spondylitis following typhoid, paratyphoid, undulant fever, and gonococcal and staphylococcal infections are well recorded, and Brailsford (1948) reports arthritis of the spine as a complication of most of the infectious diseases. Ashe and others (1941), in their review of the world's literature on Weil's disease, record meningitis, leptospiral endocarditis, peripheral neuritis, optic atrophy, and iridocyclitis as complications, but no case of spondylitis following this infection appears to have been reported.

The early radiological changes occurring in infective spondylitis may be confined to narrowing of the intervertebral disk spaces and osteoporosis of the neighbouring bone. This is later followed by loss of bony detail, small marginal erosions, and sclerosis of the opposing surfaces of the bodies, with bridging between them and possibly ultimate fusion of the vertebrae. Paravertebral abscesses may also be present.

Case History

A man, aged 59, a plumber by trade, was admitted to hospital on 13 April, 1949, with a history of lassitude and shivering attacks for a week, and jaundice for the last two days. He stated that he had been working in a rat-infested factory until a week before admission. Examination revealed a febrile, drowsy, dehydrated, jaundiced man with purpuric spots on his trunk. A clinical diagnosis of sub-acute hepatic necrosis was made.

Blood Examination.—White-cell count 13,300; agglutinations positive to *Leptospira icterohaemorrhagica* to 1 : 1,000, but negative to *L. canicola.*

Three weeks later, white-cell count 25,000; agglutinations positive to *L. icterohaemorrhagica* to 1 : 3,000, and positive to *L. canicola* up to a titre of 1 : 300. Agglutinations positive to *B. typhosus H.* to 1 : 50, but negative to *B. typhosus O*, *B. paratyphosus A* and *B*, and *Brucella abortus.*

Treatment.—He was treated with penicillin and improved after a slow and stormy course, but discharged himself from hospital on May 30, although still unable to walk. He does not remember suffering from pain in his back while in hospital, although an *x* ray of his spine taken on May 12, 1949, showed some osteo-arthritic changes in the mid-dorsal region and no other abnormality.

Later Developments.—After returning home he complained of pain across his back on attempting to get up, and he remained bed-ridden until November 16, 1949, when he was seen in the Rheumatic Unit and admitted to the wards.

Examination revealed a wasted individual with a stiff spine, tender to percussion in the lower dorsal area. All movements were limited at the right hip. On questioning he denied having suffered from pain in his hips or spine prior to this illness, saying that he had not lost a day off work for 14 years on account of illness.

Blood Examination.—Red-cell count 3,600,000; haemoglobin 74 per cent.; white-cell count 14,400; alkaline phosphatase 10 units; acid phosphatase 3·2 units; blood sedimentation rate 90; Wassermann reaction negative; agglutinations positive to *L. icterohaemorrhagica* to 1 : 100, *L. canicola* to 1 : 10, and *B. typhosus H* 1 : 25; negative to *B. typhosus O*, paratyphoid, and *Br. abortus*.

X-Ray Examination.—November 22, 1949. A considerable increase had taken place in osteophytes in the lower five dorsal and upper three lumbar vertebrae with massive outgrowths. The disk spaces in this area were all markedly narrowed with marginal erosions and loss of definition of the bone structure of the vertebral bodies. The intervertebral joints in the upper lumbar area appeared normal and there was no evidence of paravertebral abscess. The right hip was internally rotated. There were heavy osteophytic deposits on the acetabulum with erosions of the articular cartilage of the femoral head and acetabulum with some sub-articular erosions (Fig. 1). The left hip showed some degenerative changes, but not beyond normal limits for his age.

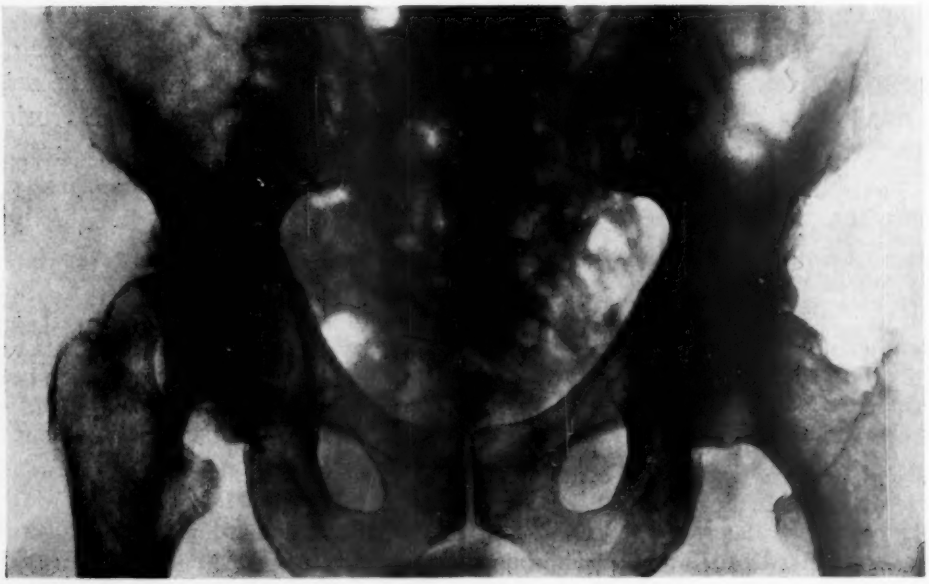

FIG. 1.—Radiograph of hips, showing osteo-arthritic changes in right hip, November 25, 1949.

Treatment.—He was given a further course of penicillin and a spinal jacket was fitted on February 10, 1950. By March 20, 1950, four months after admission, he was free from pain and able to walk in his jacket; the blood sedimentation rate had fallen to 50. *X* rays taken in July, 1950, just before discharge showed an increase in the size of the osteophytes and erosions in the vertebrae with a further decrease of the disk spaces and spread of the lesion to the seventh dorsal and fourth lumbar vertebrae (Figs 2 and 3). There were no further radiological changes in his hips.

FIG. 2.—Radiograph of spine, showing progressive narrowing of intervertebral disk spaces with ankylosis, July 21, 1950.

FIG. 3.—Lateral view of spine, showing marginal erosions, July 21, 1950.

Discussion

This patient first noticed severe pain in his back some four months after an infection with *L. icterohaemorrhagica*. The radiological appearances were those of an infective spondylitis and it is interesting to note that in both typhoid and brucellosis, spondylitis may occur many months after the original infection. Keith and Keith (1926) noted that in typhoid bony deposits may already be present in the lateral ligaments by the time the patient first complains of backache.

No films of this patient's hips before his illness are available, but he states he was able to work normally up to this time. When seen six months after his original discharge from hospital there was considerable limitation of movement in the right hip, with osteophytic outgrowths and erosions in the head of the femur and acetabulum, and it is not unlikely that these changes are similar in origin to those described in his spine.

Summary

A case of infective spondylitis with involvement of one hip following an attack of Weil's disease is described.

I should like to thank Dr. Francis Bach and Mr. H. E. Harding for their interest in this case, and Dr. Grace Batten for her considerable help with the radiology.

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Spondylite à la Suite de la Maladie de Weil

Résumé

On décrit un cas de spondylite infectieuse affectant une hanche et survenant après une attaque de la maladie de Weil.

Espondilitis Consecutiva a la Enfermedad de Weil

Resumen

Descripción de un caso de espondilitis infecciosa en una cadera, ocurriendo después de un ataque de la enfermedad de Weil.

THERMAL RESPONSE IN RHEUMATOID ARTHRITIS

BY

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It is well known that the application of heat or cold to one limb results after a shorter or longer period in an increase or decrease in the temperature of the surface of the other limbs. This response is part of the heat-regulating mechanism of the body and is due to changes in blood flow brought about mainly by dilatation or constriction of the smaller arteries and arterioles (Lewis, 1936). Indirect, or reflex, vasodilatation has been studied by Gibbon and Landis (1932), and Fatherree and Allen (1938). The mechanism has been fully discussed by Richards (1946).

The thermal vascular response is excited by the warm venous blood, returned from a limb heated by immersion in hot water, finally reaching the heat-regulating centre in the hypothalamus. Some workers claim that there are special afferent dilator fibres acting as well (Martin, 1930), in which case the mechanism would be a true nervous reflex. The existence of these dilator fibres has not been universally accepted though fibres conveying constrictor impulses do in fact exist. This may explain the greater rapidity of response to a cold stimulus. The response is effected by efferent nervous impulses and whether the pathway is actively dilator, with or without local liberation of dilator substances, or whether it is produced by inhibition of constrictor nerves, need not concern us here.

Variations can be observed in the promptness and extent of the thermal response in different patients. This can form the basis of circulatory tests as was first shown by Gibbon and Landis (1932). Benatt and Taylor (1940) used the contrast bath as a test for vascular response by immersing one arm alternately in hot and cold water and recording the skin temperature of the finger-nail bed. The recovery time from a cold application was used by Woodmansey (1946) as a test for vasomotor disturbances in rheumatism.

Indirect vasodilatation is often used as a test to determine the extent of vasospasm in considering the advisability of sympathectomy (Abramson, 1944). The test has been widely used by Richards in occlusive vascular diseases.

Method

Since environmental temperatures have a marked effect on vasodilatation in the extremities (Martin and others, 1946), in order to standardize the test a room was equipped with an electric fan for circulating an adjustable amount of cool air from outside through a heating element. The latter, controlled by a thermostat, keeps the room at a constant temperature of 65° F. (18·3° C.). This is nearly always possible except on some very hot summer days; expense precluded the installation of refrigerating plant for these few

occasions. The patient sits comfortably for at least 30 minutes with hands resting and legs exposed to the knees. Skin temperatures* are taken periodically on the plantar and volar aspects of the terminal phalanges of great toes and thumbs, and a point on the forehead. This last provided a convenient indication of body temperature, usually rising a degree or so during the test. The figure has been omitted from the graphs.

Having arrived at a stage of reasonable stability, one foot is then immersed to a depth of 15 inches in hot water at 44° C. and readings are continued at the other sites.

These particular points on thumb and toe are chosen because they are close to dense arteriolovenular anastomotic areas where local changes in the amount of circulating blood are most rapidly reflected in wide ranges of skin temperature. Other points are much less suitable. For instance, in the tests shown in Figs 2 and 5 (pp. 70 and 71), three other points were taken besides the toe:

(1) 1 inch from base of toe,
(2) on dorsum of foot,
(3) to left of tibia, 4 inches below patella.

It is clear from the curves that the toe temperature provides the most convincing criterion of circulatory change.

During the rest period there is frequently observed a rise in temperature of the hands, often quite considerable, followed by a more or less rapid fall. This is illustrated in Fig. 1 (p. 70). The rise may be explained by a normal vasodilatation induced by entry into a comfortable room with perhaps a psychological factor

* The thermocouple method was used formerly for this class of work but a recent improved apparatus made by Light Laboratories, 31a Shanklin Road, Brighton, 7, is found quicker in action and more convenient. It is based on the Wheatstone bridge principle—one resistance arm being fitted to a probe on a flexible lead, which is placed in contact with the skin at any point. The point of this probe is a minute glass capsule containing a special compound with a high temperature-resistance coefficient. The current is produced by a valve-oscillator and a three-valve amplifier ensures the accurate determination of the null point. The variable resistance is calibrated in degrees centigrade. See Bourne (1946).

TABLE I
NORMAL CONTROLS

Case No.	Sex	Age	Thermal Response			
			Delay (mins)	Rise in Temperature of Toe (°C.)	Duration of Rise (mins)	Index * (°C. per min.)
1	M.	55	21	22·6-31·2	9	0·41
2	M.	35	22	23·6-26·8	5	0·29
3	F.	18	12	21·0-28·6	15	0·36
4	F.	19	0	25·6-29·5	5	1·0
5	F.	42	7	21·6-26·7	19	0·30
6	M.	41	0	High	0	1·0
7	F.	38	6	24·4-29·2	20	0·39
8	F.	22	6	25·0-30·4	10	0·71
9	M.	22	13	23·4-31·2	10	0·53
10	F.	20	7	19·2-23·8	22	0·17
11	F.	22	0	19·0-22·0	30	0·10
12	M.	45	—	0	—	—
13	F.	24	10	20·8-31·0	20	0·4

* In all Tables cases showing a high initial temperature or a very rapid rise in the curve are arbitrarily given the index 1·0.

dependent on the temporary interest aroused by the experimental equipment and the reassurance of the pleasant nature of the test to be imposed. The subsequent cooling off may be the result of muscular inactivity and mental relaxation.

Material

Normal Controls.—Tests were made on thirteen healthy subjects between 18 and 55 years of age (Table I). This group of controls, though small, gives a fair picture of the variations to be expected.

Hands.—In eight cases the hands were warm before the immersion began; in the other five there was some degree of vasospasm, but this was speedily released in the test.

Feet.—Although in ten cases the toes were at first cold, only one gave no response and one a negligible response.

All workers in this field have recorded the fact that the lower extremities are ordinarily in a state of higher vasoconstrictor tone than the upper. Both upper and lower limbs participate in the thermoregulatory requirements of the body, but the vessels of the fingers retain a greater degree of patency in a cool environment, perhaps because they have a greater need than the toes to carry out delicate muscular and tactile functions.

As for the two persons who gave no response or a negligible one, Richards (1946) also found in certain of his normals that vasodilatation failed to occur. He quotes other investigators who had had the same experience, saying:

> This does not necessarily indicate a defect in nervous conduction or any structural change in the blood vessels of the lower extremity.

Woodmansey and others (1938) noted a failure of adaptability to the temperature changes of a contrast bath, in the hands of some otherwise apparently healthy females. It can, however, be argued that such persons though acting as normals, have a certain abnormality. In the above two cases the discomfort of unduly cold extremities was admitted.

Occlusive Vascular Diseases.—At the other end of the scale and as a basis for comparison another group was taken consisting of 51 patients from the Harrogate General Hospital with very marked circulatory inadequacy of the limbs; 43 suffering intermittent claudication and eight showing Raynaud's syndrome or other vascular defect in the upper limbs (Table II, p. 68).

Hands.—About half showed a fair or good response in the hands. The rest showed varying degrees of sluggishness or delay, but none was entirely without response.

Feet.—33 showed no response; twelve showed some delay or sluggishness; only six could be said to have reacted well (normally) and in two at least of these six, the symptoms could be attributed to psychoneurotic rather than organic disturbance.

Rheumatoid Arthritis.—76 patients with rheumatoid arthritis were tested at the Royal Bath Hospital (Table III, pp. 69 to 70).*

Hands.—Out of these at least 66 showed what might be accepted as a normal response.

Feet.—In the toes, however, 29 patients showed no response whatever and in some others the response was slow and uncertain.

* In Table III are given some additional data : duration of disease, erythrocyte sedimentation rate, plasma viscosity, and haemoglobin content, where the figures were available. A comparison of the thermal response index with each of these, however, shows no correlation whatever.

TABLE II

CASES OF OCCLUSIVE VASCULAR DISEASE

Case No.	Sex	Age	Thermal Response			
			Delay (min).	Rise in Temperature of toe (°C.)	Duration of Rise (min.)	Index (°C. per min.)
1	F.	41	—	0	—	—
2	M.	49	—	0	—	—
3	M.	52	—	0	—	—
4	M.	56	5	22·0-26·6	25	0·25
5	F.	42	7	23·2-31·4	22	0·43
6	M.	53	—	0	—	—
7	F.	73	16	24·2-31·6	5	0·60
8	M.	68	—	0	—	—
9	M.	53	0	25·2-27·6	30	0·29
10	M.	62	0	25·0-29·0	21	0·48
11	M.	49	—	0	—	—
12	M.	70	—	0	—	—
13	M.	67	—	0	—	—
14	M.	54	5	21·0-25·6	25	0·22
15	M.	52	—	0	—	—
16	M.	—	—	0	—	—
17	M.	68	7	22·2-26·2	23	0·24
18	F.	25	12	21·0-26·0	17	0·24
19	F.	—	—	0	—	—
20	M.	53	0	25·0-27·3	27	0·31
21	F.	47	—	0	—	—
22	M.	35	—	0	—	—
23	M.	70	—	0	—	—
24	M.	48	—	0	—	—
25	M.	—	—	0	—	—
26	M.	66	—	0	—	—
27	M.	73	—	0	—	—
28	M.	55	—	0	—	—
29	M.	32	10	20·0-30·0	20	0·37
30	F.	70	—	0	—	—
31	M.	61	—	0	—	—
32	F.	47	0	20·0-30·0	16	0·69
33	M.	66	—	0	—	—
34	F.	71	—	0	—	—
35	M.	62	—	0	—	—
36	M.	18	—	0	—	—
37	M.	58	—	0	—	—
38	M.	54	10	20·4-26·0	20	0·23
39	M.	46	10	20·4-27·4	20	0·28
40	F.	29	—	0	—	—
41	M.	69	15	22·0-26·0	15	0·23
42	M.	54	—	0	—	—
43	M.	62	20	26·0-30·4	10	0·38
44	F.	35	7	23·6-28·4	15	0·43
45	F.	40	—	0	—	—
46	F.	62	3	20·0-24·0	26	0·17
47	F.	41	—	0	—	—
48	F.	—	—	0	—	—
49	M.	47	13	24·2-31·0	17	0·40
50	M.	54	—	0	—	—
51	M.	61	—	0	—	—

TABLE III

CASES OF RHEUMATOID ARTHRITIS

Case No.	Sex	Age	Duration of Disease (years)	Corrected E.S.R.	Plasma Viscosity (Water = 100)	Haemoglobin (%)	Thermal Response			
							Delay (min.)	Rise in Temperature (°C.)	Duration of Rise (min.)	Index (°C. per min.)
1	F.	24	7	25	204	75	15	20·4-28·2	7	0·42
2	F.	21	11	25	211	81	22	21·2-27·6	8	0·29
3	F.	30	2	9	200	88	—	0	—	—
4	F.	21	1	11	187	86	12	20·2-23	18	0·13
5	F.	36	7	33	206	75	0	18·6-25·2	27	0·23
6	F.	24	9	19	202	70	—	0	—	—
7	F.	36	—	17	194	85	16	22·6-27·6	10	0·33
8	F.	23	2	16	200	87	12	21·4-28·4	18	0·31
9	F.	24	3	3	169	90	19	22·4-28	11	0·30
10	F.	25	1	9	187	78	22	22·4-27·9	8	0·29
11	F.	54	2	30	190	88	—	0	—	—
12	F.	34	11	32	—	72	11	24·5-30·1	14	0·44
13	F.	45	20	38	230	62	10	21·0-23·2	10	0·21
14	F.	34	1	9	180	90	—	0	—	—
15	F.	18	2	32	—	90	9	22·6-27·4	20	0·29
16	M.	46	2	42	218	84	0	High	0	1·0
17	F.	37	5	5	184	94	19	19·7-23·4	11	0·15
18	F.	37	—	8	197	84	—	0	—	—
19	F.	19	3	41	226	78	10	21·4-28	20	0·30
20	F.	23	1	43	265	76	25	20·4-24·2	4	0·18
21	M.	18	3	12	186	90	17	19·5-23	13	0·15
22	M.	15	1	9	175	100	0	25·4-29·1	20	0·51
23	F.	24	6	42	215	72	10	21·6-28	18	0·32
24	F.	15	2	3	196	67	0	24·8-32	25	0·52
25	M.	47	2	—	161	82	—	0	—	—
26	M.	42	8	36	214	84	10	20·0-27·4	14	0·35
27	M.	40	20	14	186	91	0	High	0	1·0
28	M.	52	5	43	238	90	0	High	0	1·0
29	M.	26	5	35	196	96	26	22·4-28	4	0·30
30	M.	40	1	25	192	86	13	24·4-30·8	11	0·51
31	M.	62	10	20	182	90	12	21·4-29·8	18	0·36
32	M.	49	10	34	194	84	—	0	—	—
33	M.	44	5	44	229	84	9	21·0-24·8	21	0·19
34	M.	50	10	44	227	97	26	22·6-24	4	0·17
35	M.	28	2	16	186	96	—	0	—	—
36	M.	41	1	11	—	90	—	0	—	—
37	M.	48	1	—	—	—	—	0	—	—
38	M.	26	5	4	181	96	—	0	—	—
39	M.	50	14	9	—	—	—	0	—	—
40	M.	47	5	—	—	—	—	0	—	—
41	M.	53	2	22	198	91	—	0	—	—
42	M.	34	5	—	—	—	—	0	—	—
43	M.	45	3	14	169	90	—	0	—	—
44	F.	45	20	41	—	77	10	22·0-32·2	20	0·44
45	F.	48	14	40	202	—	15	21·4-24	6	0·24
46	F.	46	13	16	184	87	14	22·8-29·6	13	0·39
47	F.	59	4	38	208	85	7	25·2-30·2	6	0·86
48	F.	45	7	10	185	87	14	22·2-30·0	14	0·32
49	F.	53	6	43	224	74	17	24·1-28·0	8	0·36
50	F.	37	1	11	200	68	0	High	0	1·0
51	F.	61	10	31	—	91	0	High	0	1·0
52	F.	53	1	30	209	—	—	0	—	—
53	F.	—	—	—	—	—	—	0	—	—

(*continued overleaf*)

TABLE III—*continued*

Case No.	Sex	Age	Duration of Disease (years)	Corrected E.S.R.	Plasma Viscosity (Water = 100)	Haemoglobin (%)	Thermal Response			
							Delay (min.)	Rise in Temperature (°C.)	Duration of Rise (min.)	Index (° C. per min.)
54	F.	23	3	6	171	—	—	0	—	—
55	F.	40	8	40	200	80	0	High	0	1·0
56	F.	51	10	45	214	80	—	0	—	—
57	F.	50	10	42	231	91	—	0	—	—
58	M.	37	6	42	216	85	—	0	—	—
59	M.	58	15	—	—	—	—	0	—	—
60	M.	34	7	44	248	104	—	0	—	—
61	M.	53	—	28	191	104	—	0	—	—
62	M.	55	30	42	218	95	2	20·4-29·0	28	0·33
63	F.	40	12	8	168	84	—	0	—	—
64	F.	39	6	22	188	91	21	19·6-30·2	9	0·37
65	F.	44	3	13	186	86	20	21·6-29·8	9	0·37
66	F.	51	2	42	242	74	—	0	—	—
67	F.	—	—	—	—	—	—	0	—	—
68	F.	25	1	35	196	—	11	17·4-25·6	19	0·22
69	M.	43	9	20	177	—	13	20·0-24·0	16	0·17
70	F.	19	9	2	179	—	15	21·6-30	4	0·58
71	M.	34	3	13	184	—	21	19·8-29·0	6	0·37
72	M.	42	1	—	—	—	—	0	—	—
73	M.	42	12	4	168	—	1	21·8-28·2	12	0·71
74	M.	20	6	16	—	—	23	21·4-29·4	7	0·35
75	F.	33	—	—	—	—	20	22·8-32·2	10	0·41
76	F.	—	—	—	—	—	22	22·0-23·8	8	0·16

Discussion

As vasoconstrictor tone appears to be almost as readily released under the strong influence of a thermal stimulus in the upper limbs of rheumatoid arthritics

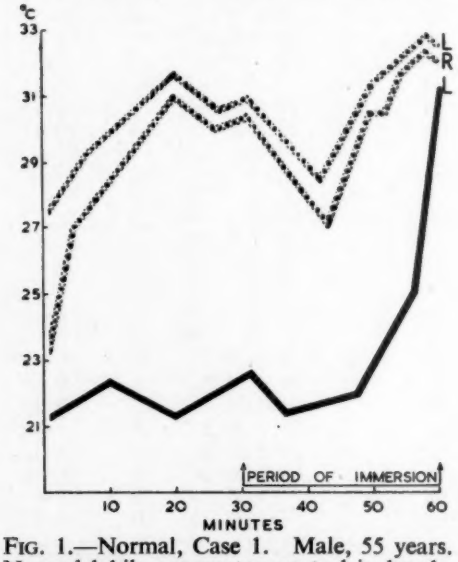

FIG. 1.—Normal, Case 1. Male, 55 years. Normal labile vasomotor control in hands. Toe cold at beginning, but response complete.

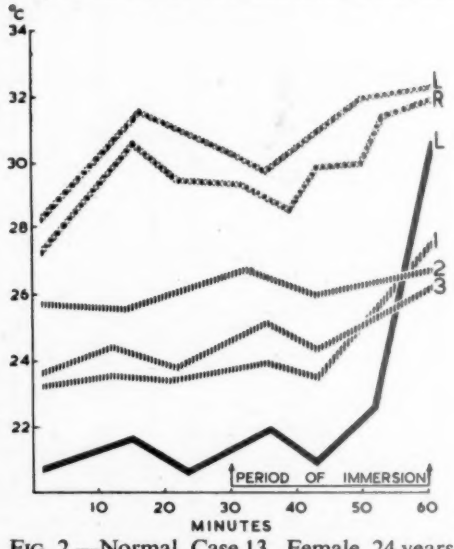

FIG. 2.—Normal, Case 13. Female, 24 years. Active vasodilatation in hands; toe cold at beginning, but response rapid.

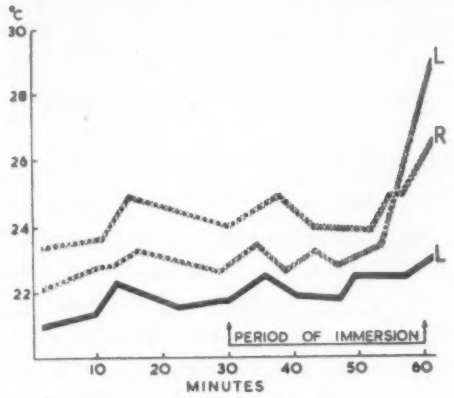

FIG. 3.—Occlusive vascular disease, Case 1. Female, 41 years. Erythrocyanosis. Delay in response in hands; no response in toe.

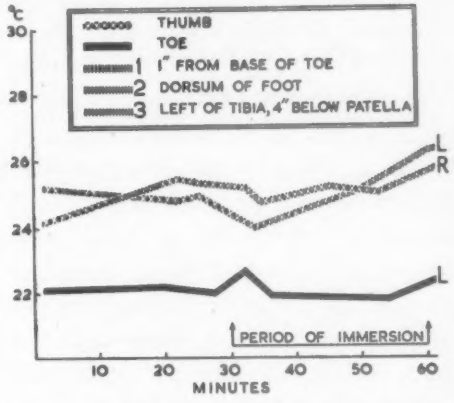

FIG. 4.—Occlusive vascular disease, Case 26. Male, 66 years. Buerger's disease. Little, if any, response in hands; no response in toe.

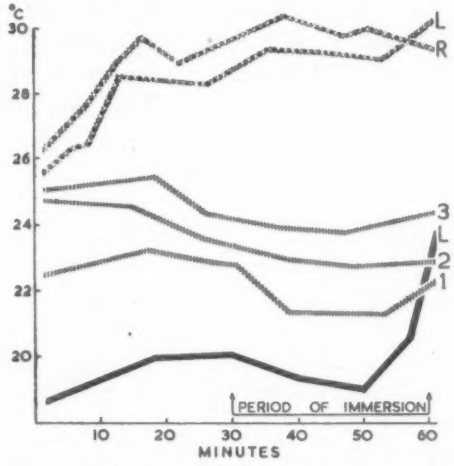

FIG. 5.—Rheumatoid arthritis, Case 17. Female, 37 years. Active vasodilatation in hands; response in toe delayed and small in extent.

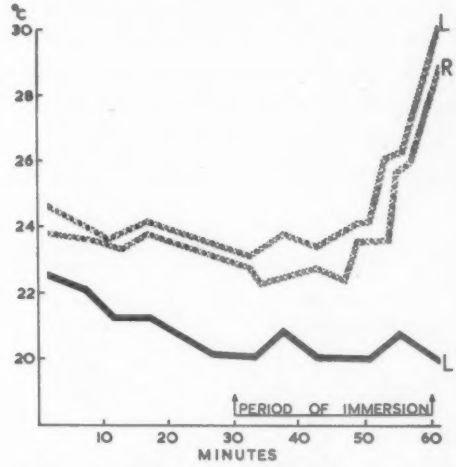

FIG. 6.—Rheumatoid arthritis, Case 41. Male, 53 years. Active response in hands; none in toe.

as in those of healthy people, in this study we confine our attention, in the Tables of results, to the toes, from which more information may be gathered.

Diagrams.—From each group two typical graphs are shown (Figs 1-6). In the examination of a graph (limiting our attention to the curve of toe temperature, solid black line) the features to be noted are:

(1) The delay between the time of immersion and the time the rise commences. This delay may depend on the degree of vasospasm at the outset and the promptness or sluggishness with which this vasospasm is released in the immersed limb, for the efferent impulse is not initiated until sufficient warm venous blood returns. The presence of much or little subcutaneous body fat seems of little account as an insulator.

(2) The extent of the rise. This presumably depends upon the degree of vasodilatation of which the peripheral vessels are capable.

(3) The time lag between the initiation and completion of the rise. The rise may show a steep or shallow gradient. One might suggest that the latter signifies a sluggish vasodilating mechanism at the efferent end.

An attempt has been made to calculate a single figure index of thermal response, but it is difficult to incorporate all the factors concerned.

For instance, a curve may pursue a horizontal course for 20 minutes and then rise steeply in 4 or 5 minutes from 20° to 27°. Another may begin rising almost immediately from 20° to 27° in a uniform but shallow gradient. It is realized that the physiological mechanism involved in the two cases must differ and that the difference may be of diagnostic significance. Yet if the time required to attain the peak is the same, there is justification for giving these two curves the same index because the final degree of vasodilatation is apparently the same.

For this "Index of Thermal Response" the most satisfactory compromise seems to be to use a figure expressing the average gradient (in fractions of a degree per minute). The rise is measured from 19° (the nearest whole number of degrees above room temperature). Thus a rise from 25° to 29° is given the same value as a rise from 20° to 29°, as it is considered that the partial initial vasodilatation should not be prejudicial to any numerical assessment. The results (Table IV) show the figures for rheumatoid arthritis to be intermediate between the normal state and that of established occlusive vascular conditions. A high incidence of a peripheral vasomotor defect is shown in patients with rheumatoid arthritis.

TABLE IV
SUMMARY OF RESULTS

Thermal Response		Normal Controls		Occlusive Vascular Disease		Rheumatoid Arthritis	
Grade	Index	%	Number of observations	%	Number of observations	%	Number of observations
Absent or poor	0 to 0·1	15·4	2	64	33	38·2	29
Fair	0·1 to 0·5	53·8	7	32	12	46·0	35
Good	above 0·5	30·8	4	4	6	15·8	12

Summary

(1) A simple method of carrying out a thermal response test is described.
(2) Results of tests on 76 patients with rheumatoid arthritis are tabulated.
(3) Evidence is shown of the high incidence of a vasomotor defect in this disease.

The author's thanks are due to the consultants at the Royal Bath Hospital, Harrogate, and the Harrogate General Hospital for sending patients, to Dr. G. N. Myers, Director of the Regional Rheumatism Research Unit, who has approved the routine use of the test for his patients, and to Dr. Douglas H. Collins for his interest and helpful discussions over many years.

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La Réponse Thermale dans l'Arthrite Rhumatismale

RÉSUMÉ

(1) On décrit une simple méthode pour effectuer l'épreuve de la reponse thermale.
(2) On énumère les résultats de cette épreuve chez 76 malades atteints d'arthrite rhumatismale.
(3) On démontre la grande fréquence de l'insuffisance vasomotrice dans cette maladie.

La Respuesta Termal en la Artritis Reumatoide

RESUMEN

(1) Descripción de un simple método para efectuar la prueba de la respuesta termal.
(2) Tablas de los resultados de esta prueba en 76 enfermos con artritis reumatoide.
(3) Demostración de la gran frecuencia del defecto vasomotor en esta enfermedad.

HEBERDEN SOCIETY

ANNUAL REPORT, 1950

The Society has had a successful year of work. The membership is now at the maximum of 100, two members having resigned and nine applicants having been admitted during the year, and there is still a waiting list for membership. The new *Honorary* Members are Professor Hans Selye and Professor F. Coste, who respectively gave the Heberden Oration and the Heberden Round.

The first meeting was held at the Westminster Hospital on January 6, 1950. The members were welcomed by Sir Arnold Stott on behalf of the Honorary staff, and some most interesting cases were shown by Dr. Dudley Hart and his colleagues. (See *Annals*, March, 1950, **9**, 73).

On March 10 members travelled to Manchester, where Dr. J. H. Kellgren's department, the Nuffield Rheumatism Research Centre, Royal Infirmary, acted as host, and a number of valuable and interesting demonstrations and papers were presented by Dr. O. Janus and others. Professor S. L. Baker described an unusual type of bone disease. A visit was made on March 11 to the Walkden Colliery Clinic, where an inquiry into the incidence of the various types of chronic rheumatic disease is being conducted by Dr. J. S. Lawrence. (See *Annals*, June, 1950, **9**, 178.)

On May 20 the Society took the unusual step of voyaging as far as Paris for the annual Heberden Round, which was ably conducted by Professor Coste, the first University Professor of Rheumatology to have been appointed in Europe. An official account of this very enjoyable week-end function appeared in the *Annals* (September, 1950, **9**, 249). About fifty members and their friends attended the meetings at the Hôpital Cochin. The social functions included a splendid luncheon party at Professor Coste's house, a reception by the British Council, and an official lunch at Enghien on the Sunday.

The Heberden Oration on " The Rheumatic Diseases as Diseases of Stress ",* was delivered by Professor Hans Selye, of the Institute of Experimental Medicine and Surgery, Montreal, on June 2 and 3, at B.M.A. House (by kind permission). In view of the unusually wide interest shown, it was decided to admit all medical visitors. Nearly 300 turned up, and an overflow meeting was held in another hall. Votes of thanks were proposed by Lord Moran (Honorary Member) and Sir Henry Cohen (President-elect). The Ciba Foundation later gave a cocktail party at which members were welcomed by Lord Beveridge, and were able to meet their Orator informally.

On October 5, our Honorary Member, Dr. P. S. Hench, lectured for the second time before the Society at the West London Hospital, his subject being " The Present Status of Cortisone and ACTH in the Treatment of the Rheumatic Diseases ". In the evening the Council of the Society entertained him and Mrs. Hench to dinner at the Athenaeum, their health being proposed by Lord Horder. The Society sent Dr. Hench their congratulations upon the award made to him shortly afterwards of the Nobel Prize for Medicine, which he shares with Dr. E. C. Kendall, who is to be the Heberden Orator for 1951.

At the invitation of Dr. E. G. L. Bywaters, members visited the Rheumatic Department of the Canadian Red Cross Memorial Hospital at Taplow, on October 21, where several interesting cases were shown. (See *Annals*, December, 1950, **9**, 382.)

At the Annual General Meeting held on December 8 and 9, Professor E. C. Dodds

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* The first part of the Oration was reported in full in *Brit. med. J.* (1950), **1**, 1383, and the second part was summarized in the *Annals* (September, 1950, **9**, 246).

and Dr. Peter Bishop presented a symposium on modern endocrine work and its application to the rheumatic diseases.* A report of the second day's meeting appears below (page 76).

The annual dinner was held at the Apothecaries' Hall by kind permission of the Master (Dr. F. Howitt), a past-President of the Society. The guests of honour were Lord Reith, who responded to the toast of the visitors wittily proposed by Dr. Heald, and Sir John Charles, Chief Medical Officer of the Ministry of Health, who proposed the health of the Society, to which the President replied. Dr. F. Françon, the doyen of French rheumatologists, was also a guest.

Several gifts have been received into the library during 1950. The most notable is a copy of *Opera Omnia Medica*, by Guillaume Ballonii (Ballonius), dated 1762, volumes I, II, III, and IV, generously purchased and presented by Dr. Ernest Fletcher. The following were presented by St. Thomas's Hospital :

Marsh, H., " Diseases of the Joints and Spine " (1895).
Thomson, F. G., and Gordon, R. G., " Chronic Rheumatic Diseases " (1926).
Poynton, F. J., and Schlesinger, B., " Recent Advances in the Study of Rheumatism " (2nd ed., 1937).

The following were presented by Dr. W. S. C. Copeman :

Jones, E. G., " An Account of the Eau Medicinale d'Husson in the Gout " (2nd ed., 1810).
Barlow, E., " An Essay on the Medicinal Efficacy and Employment of the Bath Waters " (1822).
Falconer, W., " Dissertation on the Medicinal Effects of the Bath Waters " (1740).
Roberts, W., " On the Uric Acid Gravel and Gout " (1892).
Marsh, H., " Septic Arthritis " (1903).
Haden, C. T., " Practical Observations on the Colchicum Autumnale " (1820).

In addition, Rodamel, P. M., "Traité de Rhumatisme Chronique" (1808), was purchased by the Society.

The Ciba Foundation have kindly offered to house the library at their house at 41 Portland Place, W.1, without fee. Members will be notified when the books have been transferred. It is hoped that members will continue to present to the library any books or relics of rheumatic interest dating from prior to 1900.

The Draft Programme for 1951 includes the following:

April 6. Clinical Meeting at the Royal Free Hospital, London.
Presidential address by Prof. Sir Henry Cohen in the evening at 41 Portland Place, W.1.
May 10. Heberden Round at the Royal Infirmary, Edinburgh.
July 27. Meeting at 41 Portland Place, W.1.
December 7 and 8. Annual General Meeting.

It is probable that additional meetings will be arranged during September and October when certain distinguished Americans will be visiting Great Britain.

Titles and summaries of original communications which members wish to make to the Society during 1951 should be sent to the Senior Hon. Secretary (Dr. F. Dudley Hart), together with an abstract not exceeding fifty words, at least one month before the date of meeting. Additional meetings will be arranged if necessary. Abstracts of papers delivered are published in this Journal.

Annual General Meeting.—The meeting opened in the Meyerstein Theatre, Westminster Medical School, on December 8, 1950. The President, Dr. W. S. C. Copeman, was in the chair, and papers were read by Prof. E. C. Dodds and Dr.

* These papers were reported in *Brit. med. J.* (1950), **2**, 1488.

Peter Bishop (see page 75). When the meeting was continued in the Meyerstein Theatre on December 9, 1950, a series of five papers was presented.

(1) **Dr. F. Françon** (*Paris*) read a paper on " Psoriatic Arthritis ". He stated that the condition was not a very frequent one but that every physician met several cases in the course of a year's work. He considered that about 7 per cent. of patients with psoriasis developed arthritis, the male/female ratio in his series being 2 to 3. It was seldom seen before 30 to 45 years of age, and in most cases psoriasis preceded the arthritis. Usually there was no connection between the seat of the psoriasis and the seat of the arthritis, though this was occasionally noted. The " sausage finger " with all the joints of one or several fingers affected was not uncommon. Although many types of arthritis might be associated with psoriasis, rheumatoid arthritis was the most common and the greatest problem. Two groups might be differentiated : the first with insidious onset starting in the small peripheral joints of the fingers with anaemia, muscle wasting, and loss of weight ; the second and more frequent, affecting large and small joints and presenting more abruptly as an acute arthritis. Both types tended to run a chronic course.

The blood urea, chlorides, serum proteins and plasma uric acid, and calcium phosphate are normal in psoriatic arthritis ; the serum cholesterol tends to be below the normal level ; the basal metabolic rate is normal ; radiologically there is no picture pathognomonic of psoriatic arthritis.

For treatment Dr. Françon advocated injections of gold or copper, together with routine treatment in common use for rheumatoid arthritis.

(2) **Dr. James Reid** read a paper on " The Clinical and Biochemical Changes in Rheumatism ". He said that the abnormal changes in acute rheumatism were not well known. An attempt had been made to find out what they were by investigating simultaneously biochemical and clinical alterations during treatment of an acute attack of rheumatic fever with salicylate. The findings were briefly as follows : the disappearance of acute rheumatic manifestations such as fever, tachycardia, and acute arthritis was associated with the transfer of water from cells to extracellular fluids, an over-all increase in nitrogen and potassium excretion, and the retention of sodium and chloride. At this point the patient had passed from the acute rheumatic to the convalescent phase in which the principal features were weakness, easy fatiguability, and a high erythrocyte sedimentation rate. The transition from the convalescent phase to normal, indicated by a progressive fall in the erythrocyte sedimentation rate, was associated with the removal of excess water from the body by diuresis, an over-all increase in the excretion of sodium and chloride, and a diminution in nitrogen and potassium output.

The discovery of Hench and his colleagues of the importance of cortisone and ACTH in rheumatism strongly suggested that the adrenal cortex was concerned with natural remission. Furthermore, the main clinical and biochemical changes resulting from the administration of ACTH and cortisone or salicylate were the same. The relief of acute rheumatic manifestations was associated with increased nitrogen and potassium excretion. The suggestion that salicylate and cortisone and ACTH had a common action was further strengthened by the observation that in addition to similarity in clinical and biochemical effects the side effects were also identical. Salicylate could produce a mild Cushing's syndrome, face swelling, and acne.

In conclusion, Dr. Reid suggested that the anti-rheumatic action of cortisone, ACTH, and salicylate were the same, bearing in mind the role which the adrenal cortical hormones played in the regulation and distribution of the water. It might well be that the manifestations of acute rheumatism were simply expressions of an abnormal fluid shift resulting from disorders of protein and probably electrolyte metabolism.

The President said that Dr. Reid's paper was an extremely good example of the new functional outlook on the study of disease, in which he thought they could say that rheumatologists both in America and in the United Kingdom were leading the way.

Prof. R. E. TUNBRIDGE said that Dr. Reid in discussing the transfer of fluid did not give any figures for the extracellular fluid, or mention the effect of sweating. Sweating had a very pronounced effect on fluid balance and could account alone for some of his figures.

Dr. C. B. HEALD asked whether the blood levels had been taken during the course of the fever and the remission, and whether they followed or synchronized with any of the changes of which he had spoken.

Dr. B. LUSH asked whether Dr. Reid had studied the effect of salicylates in normal controls.

Dr. W. A. BOURNE asked whether Dr. Reid had considered the liver function. He wondered whether there might be some function in the liver which could account for the changes observed in the glucose-tolerance curve.

Dr. REID, in reply, said that he had not had time that morning to discuss all the details of his investigation of fluid balances, but that these had already been published. With regard to the question of sweating, Prof. Tunbridge was quite right, they had no ideal method of estimation, but they could through the changes of the plasma obtain precise information as to the direction. They were perfectly prepared to stand by the qualitative findings, but as to the precise quantitative findings they did not yet know the answer in water balance.

In reply to Dr. Heald, the plasma salicylate levels had been estimated and at the height of treatment when the symptoms were most marked the plasma salicylate was also most marked. In reply to Dr. Lush, he did not know of any investigation in which salicylate had been given to normal controls and the carbohydrate tolerance decided, but in certain cases salicylate given to normal controls had produced the respiratory and other effects seen in patients with acute rheumatism who were under treatment. He expected that it would have the same effect on carbohydrate metabolism though possibly to a less degree.

As for liver function, in reply to Dr. W. A. Bourne, they had noticed falls in plasma prothrombin and even bleeding. The question about the zinc sulphate test he could not answer. He did not know whether it might have some bearing on the diminished carbohydrate tolerance. All he could say was that, since they had made this observation, every patient who had come into their wards had had his carbohydrate tolerance tested and at the height of the treatment, whatever drug they were using, and in convalescence, these changes went on.

(3) **Dr. Francis Bach** read a paper on " Splenectomy in Rheumatoid Arthritis ".* He suggested that the spleen be considered as an endocrine instrument which possibly played a role in the mechanism of rheumatoid arthritis. Between 1930 and 1937 splenectomy had been performed in a number of people suffering from Still's disease and two or three such cases had been reported from the United States and also from France. In 1938 the spleen was removed in three of his patients suffering from rheumatoid arthritis in an active and advanced stage. The clinical improvement following splenectomy impressed him, and two more patients were subjected to this operation. In 1945 he reviewed his splenectomy patients and found that clinically they had not done too badly, and he asked his surgical colleagues to try the procedure once again. The spleen appeared to exercise an inhibitory influence on the bone marrow. A review of the literature suggested an inter-relationship between the spleen and the pituitary, the spleen and the ovary, the spleen and the bone marrow, and finally the spleen and the adrenal cortex.

In the first group of patients operated on 12 years ago was one who had severe rheumatoid arthritis which had remained relatively inactive ever since. The fire had gone and the patient was left with the ashes of the disease. The other two were similar. Of the two patients operated on in 1944-45, one, a girl, also showed that the rheumatoid arthritis had since remained inactive. Seven more patients had been operated on in the late summer of 1949, and he hoped that Dr. Jacobs would say something about them. Clinically, the disease had been relatively—and in some instances completely inactive since operation ; in no instance had there been a definite flare-up. In every case the

* This paper will be published in greater detail in the next issue of this Journal (June, 1951).

removed spleen was large, in general there was a non-specific lymphoplasia, and in some there had been definite hyaline changes in the central corpuscles.

Dr. J. H. JACOBS then showed photographs relating to a number of the cases. Four had improved, and one showed a slight relapse, but was better than before the operation. In all cases the sedimentation rate had fallen. He added that they made no claim for this form of therapy which they considered experimental in nature. They were the more disinclined to make any definite claim as they had no comparative series of patients who had been operated on for other causes. However, they hoped that some light was thrown on the progress of the disease.

Dr. G. D. KERSLEY said that he had had one extremely interesting case in 1945. This was a patient who came back from the Continent and was one of the worst cases of acute rheumatoid arthritis he had ever seen. He eventually finished up " a bag of bones ". In the last resort they removed his spleen and from that moment he improved and never looked back. The sedimentation rate went back to normal and he had made a complete recovery.

They had also taken the spleen out in another case only two days ago. This patient had been under treatment for a year and had steadily gone downhill until he was almost moribund. It was, of course, too soon to say anything about the result. He did not claim that in the first case, which appeared to be a miracle, the splenectomy was the actual cause. The stimulus of the operation might have had something to do with it, for in another instance a bad rheumatoid case had developed an acute abdomen and had been operated on, and since the operation had been completely free from rheumatic pain for the first time for many months.

Prof. TUNBRIDGE said he would like to give the other side of the picture. He had a case of leucopenia with typical marrow changes and splenectomy was recommended. Within ten days of the operation the patient developed rheumatoid arthritis. That was nine months ago.

Dr. T. G. REAH described a case which flared up with acute rheumatoid arthritis two months after operation, and it was now just beginning to subside.

Dr. O. SAVAGE referred to the interesting amyloid changes in the spleen which had also been reported from the United States.

Dr. BACH, in reply, said that Prof. Tunbridge's case bore out a point he had desired to stress. He urged members not to perform splenectomy on the strength of the cases he had mentioned, but to regard the experience as showing that the endocrine orchestra was not playing in tune. He felt, however, that the follow-up in these few cases (who were still alive and who were quite active people) might well be enough to encourage a more detailed study of the inter-relationship of the endocrine system, and especially the spleen, the adrenal cortex, and the bone marrow.

(4) **Dr. R. M. Mason** read a paper on " Familial Ankylosing Spondylitis ". He described a family in which there were three established cases of ankylosing spondylitis with clinical and radiological confirmation, one suspected case, and two presumptive cases. The patients were under the care of Dr. Copeman. He proposed to describe them in the order in which they were discovered. The first two positive cases were in sisters and in a brother the condition was suspected. The father was found to have a positive condition, and two presumptive cases, the maternal grandfather and a maternal great aunt, were found in the father's ancestry. The presumption was that the disease was transmitted to him by his mother.

All these people lived in Cambridgeshire, and one could not exclude the possibility that the environment might contain the operative factor, even though this was unlikely. One conclusion was that one should seriously consider examining and taking *x* rays of the sacro-iliac joints as a routine in all close relatives of such a patient.

A Member referred to a case of two sisters with definite ankylosing spondylitis. They belonged to a family of five brothers and four sisters and he had tried to follow up the other members, but only one had turned up at hospital and in him there were no signs discoverable at all. Apparently, however, three of the brothers had died of disease and there was also incidence of goitre in the family. The two cases in which spondylitis was found had an enlarged thyroid.

Another Member said that in the Leeds rheumatism survey there was an incidence of ankylosing spondylitis of 0·1 per cent. of the population, which fitted in with other similar figures. Two

cases in one family might be expected to occur in ten families in the same district. The occurrence of three cases he would think very unlikely.

Dr. F. DUDLEY HART referred to two brothers both of whom were spondylitics, one having developed spondylitis at about the age of 17.

Dr. H. F. WEST referred to another instance of spondylitis in both father and child. In the Bristol survey there were nine families with more than one member affected, but in only one instance was the parent affected. He also described a case in which the brother and sister of a certain professor of medicine in Great Britain both had spondylitis. That suggested a familial character, but it was found that as children they had played with the child of a neighbour who had severe ankylosing spondylitis, which might possibly suggest an environmental influence. All the Bristol families had been carefully traced, but no connection could be found between them, either as relatives or neighbours.

(5) **Dr. C. J. M. Clark** read a paper on " The Assessment of Psychological Factors and Pain in Rheumatoid Therapy ".* He referred to the importance of psychological factors in influencing the nature and severity of symptoms in rheumatoid arthritis. He suggested that alteration in the intensity of pain appreciation affected joint pain, tenderness, and range and performance tests. He described suggestions for their elimination in the evaluation of trials of therapeutic substances in rheumatoid arthritis.

To avoid interference by psychological factors in experimental investigations the following precautions were necessary : (1) To establish as far as possible neutrality on the part of all concerned in the trials ; (2) to use an inert control substance the identity of which was unknown to the patient and to all who came in contact with him ; (3) to impose a preliminary period of observation and assessment during which, if he was an in-patient, the patient would settle down in hospital ; (4) to make a simultaneous assessment of all available objective data, such as measurements for joint swellings, temperature observations, and laboratory tests.

Dr. C. E. QUIN said that the recent controversy over the effect of ascorbic acid injections had focused attention on psychological factors in treatment. Dr. Mason and he had investigated a series of 43 cases with ascorbic acid together with control injections with saline. They had recorded subjective impressions one hour after injection. Though, as in Dr. Clark's series, no specific therapeutic effect was demonstrated, there was subjective improvement in many cases. Eighteen patients stated that there was diminution of pain after injection of ascorbic acid or saline, and others that they could move more easily, although the pain was not diminished. Since they were dealing with out-patients and had to have them up for a special session, the patients waited for one hour after their injection before re-testing, and it was difficult for many people not to adopt an introspective attitude in such circumstances. However, subjective improvement occurred to an equal extent both after control and test substances.

He was interested in Dr. Clark's observation of the eosinophil count done to exclude the ACTH effect. These observations and the occurrence of improvement in less than one hour were against this possibility, particularly in the case of the patient who leapt out of bed after the injection. The effect of the ascorbic acid or saline injections seemed to be primarily psychological in origin, and not to be due to hormonal influences.

Dr. W. A. BOURNE said that, with regard to subjective assessment, he thought it helpful to have two or three independent interviews over a period of 12 or 18 months. He made it a rule in his clinic that the patient should give his own assessments to the almoner, and that the results of graded exercises should be compared with the patient's statements.

Dr. H. BURT said that in giving an injection such as ascorbic acid there did appear to be marked and immediate improvement in subjective signs. A considerable degree of spasm was present in some of these cases and it was possible that arterial spasm in the muscle caused pain. If circulation were enhanced in the muscle the blood flow was improved and the spasm relieved. There was an important psychical factor here which was not yet fully understood.

Dr. J. H. H. GLYN said that if an improvement wore off as the treatment went on, one might assume the initial improvement to have been of psychological origin. The effects of true clinical improvement should be cumulative from the first injection.

* This paper will be published in greater detail in the next issue of this Journal (June, 1951).

Dr. CLARK, in a brief reply, said that although he had mentioned certain relationships of psychological factors and pain, he by no means understood the subconscious mechanism underlying these psychological factors. Some patients improved even though they had no faith in the remedy. Nor did he know how or why the placebo effect wore off. If the original stimulus was not reintroduced, eventual condition stimuli seemed no longer able to elicit the response. Among the factors of this placebo response which one did not understand was the latent period ; why did some patients respond to one type of placebo and not to others ? ; why, if an effect wore off, should it not wear off progressively ?

The President, in closing the meeting, thanked the authors and commented on the high quality of the papers.

Clinical Meeting.—The Society held a meeting in the Meyerstein Theatre, Westminster Medical School, on January 24, 1951. The President, Sir Henry Cohen, was in the chair. A short film on the therapeutic effects of cortisone was shown by Dr. J. H. H. Glyn for Dr. W. S. C. Copeman and Dr. Oswald Savage. Sir Henry Cohen congratulated Dr. Phil Sattin, who had photographed the cases, on the high quality of the film.

After the film the following cases were shown :

(1) Acromegaly with ? Ankylosing Spondylitis (shown by Dr. F. Dudley Hart). This patient, a female 54 years of age, had been shown a year ago at the meeting. Since that time the peripheral joints had become affected, particularly the knees. As oblique views of the sacro-iliac joints showed only para-arthrodial osteosclerosis, members were asked whether this was a case warranting a double diagnosis or whether all the changes were due to acromegaly. Dr. J. H. Kellgren favoured the latter, pointing out, however, certain atypical radiological features. Dr. E. G. L. Bywaters also spoke.

(2) Osteoporosis, a Case for Diagnosis (shown by Dr. Denis Irwin). This case had also been shown the previous year. Members agreed that little further could be said as to diagnosis until a bone biopsy had been performed. Although associated with hypogonadism, the use of calciferol in treatment had produced more relief to date than testosterone given over a period of a month.

(3) Shoulder-Hand Syndrome (shown by Dr. C. J. M. Clark). A man aged 65, recently under the care of Dr. W. E. Lloyd, developed bilateral changes in the hands following acute coronary occlusion. The first sign to appear was a persistent erythema of both palms. Sir Henry Cohen and Drs. Bywaters, Kellgren, and Good joined in the discussion.

(4) Reiter's Syndrome unresponsive to Cortisone Therapy (shown by Dr. C. J. M. Clark). A girl, aged 20, at present under the care of Dr. W. E. Lloyd, had a history suggestive of Neisserian infection, though all investigations were consistently negative. Iridocyclitis followed purulent conjunctivitis, with profuse vaginal discharge and a very painful arthritis affecting feet, ankles, knees, hands, elbows, and shoulders, as well as thoracic and cervical spine. Keratodermia developed subsequently. After penicillin and aureomycin had proved of no avail a 12-day course of cortisone was given. Fresh joint involvement, in particular the inter-phalangeal joints of one thumb and several toes occurred during cortisone therapy which failed to give any improvement.

Sir Henry Cohen said that he had noted improvement on aureomycin in one case under his care. Dr. E. G. L. Bywaters said that although Reiter's disease was a dangerous diagnosis in a female, the distribution of affected joints in this case was typical ; he suggested fever therapy. Dr. Hart said that he felt that more than one aetiological agent could be responsible for this syndrome ; in this particular case he suspected, entirely on

indirect evidence, that the aetiology was gonococcal. The failure to respond to cortisone was interesting in view of the three cases recently successfully treated in Toronto.

(5) **Sjogren's Syndrome** (shown by Dr. F. Dudley Hart). A woman, aged 64, recently under the care of Dr. J. L. Lovibond, differed from most of the cases reported by Sjögren in that she looked younger than her age. She had suffered from kerato-conjunctivitis sicca and dryness of nose and mouth for 20 years. Arthritis had developed within the last three years and was still active and progressing. Dr. Hart asked if there was any evidence that such cases were anything more than a chance association of kerato-conjunctivitis sicca and rheumatoid arthritis.

Dr. J. H. Kellgren spoke of recent work in the Rheumatism Research Centre in Manchester. He had found that about 10 per cent. of elderly rheumatoids and a somewhat lower percentage of non-rheumatoids had dry eyes. Dr. W. A. Bourne commented on the absence of teeth, oral sepsis being common in these cases.

Sir Henry Cohen, in closing, thanked Dr. Dudley Hart for arranging the meeting and the Westminster Medical School for the use of the Meyerstein Theatre.

EMPIRE RHEUMATISM COUNCIL

FOURTEENTH ANNUAL REPORT

The fourteenth annual report of the Empire Rheumatism Council was presented by the Chairman, Lord Horder, at the Annual General Meeting held on January 24, 1951.

Research.—Referring to the Council's investigation into the aetiology of rheumatoid arthritis concluded in 1949, he conveyed to the Journal Committee of the British Medical Association the Council's deep appreciation of their kindness in publishing the Report as a supplement to the *Annals of the Rheumatic Diseases*. The Report should thus reach a wide field and prove a valuable document.

It was felt that some advantage might accrue from undertaking specific enquiries into the genetic factors connected with the causation of rheumatoid arthritis, and this work had been undertaken by Dr. G. M. V. Johns. Certain new facts had come to light, but were not felt to be sufficiently important to warrant an intensive continuance of the enquiry at the present.

A study of the allergic aspects of rheumatism, conducted by Dr. K. Maunsell under the able direction of Professors Rimington and Cameron, had been concluded at the Council's laboratory at the Hospital of St. John and St. Elizabeth. This had freed the laboratory for new tasks, and during 1950 the Council had been fortunate in appointing as its research worker there Dr. A. A. Henly, Ph.D., Roche Fellow of the Council, who, with his assistant, Miss M. I. Potter, was studying the metabolic effects of various steroid hormones and related substances in rheumatoid arthritis.

The Cortisone Committee of the Council had decided to publish a critical quarterly, *Annotated Bibliography of Cortisone, ACTH, and Related Hormonal Substances*, and the first issue appeared in 1950.

In connection with a special research scheme instituted at the Royal National Hospital for Rheumatic Diseases, Bath, a grant of £400 had been placed at the disposal of Dr. G. D. Kersley, the Physician-in-Charge. This grant had met the payment of a laboratory technician, Mr. D. S. Bidmead, to assist in an investigation into the effect of insulin-produced hypoglycaemia in the treatment of rheumatoid arthritis and the use of a number of compounds in the treatment of gout. Mr. Bidmead had, incidentally, evolved an improved method of estimation of uric acid in the blood and urine.

In response to an application for assistance from Professor Maclagan, of the Westminster Medical School, in research into the synthesis and trial of new compounds related to salicylic acid, with the collaboration of Dr. F. Dudley Hart, a liberal grant had been made by the Council, enabling Dr. J. D. Billimoria to be appointed as from February 1, 1950, and good progress had already been made towards the preparation of cortisone analogues.

The Chairman said he was glad to announce the receipt of a substantial discretionary legacy awarded to the Empire Rheumatism Council for the institution of research fellowships. It had been decided to establish two research fellowships to investigate the aetiology and pathogenesis of ankylosing spondylitis. The " Elizabeth Macadam Fellowships ", tenable for two years, had been awarded to Dr. G. Loewi, working at the Canadian Red Cross Memorial Hospital, Taplow, under the direction of Dr. E. G. L. Bywaters, and Dr. J. L. Potter, working at the Northern General Hospital, Edinburgh, under the supervision of Dr. J. J. R. Duthie.

Financial assistance had also been accorded to Mr. A. J. Whiten, F.R.Met.S., in furthering his investigation into the climatic effects in regard to rheumatism in general.

In no year since the Council's formation had there been a period of greater endeavour in research undertaken by the Council, commensurate with the funds at its disposal. The Finance Committee had made an allocation of £5,000 for 1950-51 in addition to the medical expenditure to which the Council was already committed, and it was probable that the sum to be expended on research and educational activities in 1950-51 would be the largest in any year since the Council's inception.

Education.—To ascertain what rheumatic treatment facilities existed in the Regional Hospital Board areas, the Education Sub-Committee had written to the Regional Hospital Board area representatives on the Council. The replies dealt mainly with existing facilities ; it was found that in most areas no growth of facilities had occurred since the inception of the National Health Service Act, 1946, although many Regions had schemes " under consideration " for the establishment of Rheumatism Units. This matter deserved further attention.

In response to an invitation from the President of the Royal College of Physicians, the Education Sub-Committee had provided the following definition of a " Specialist in Rheumatic Diseases " which might prove helpful to the newly-constituted Committee of the Royal College of Physicians (see page 84) :

> The specialist in Rheumatic Diseases should be a general physician who is specially interested in the diagnosis and treatment of morbid conditions of the limbs and trunk, due to disorders of the bones, joints and connective tissues ; and in the practice of certain therapeutic techniques. The " Rheumatologist " is therefore a general physician of consultant status with a special interest. Thus he is comparable with the neurologist or cardiologist. The specialty in Rheumatic Diseases is distinct from the specialty in Physical Medicine.

The circulation of the *Annals of the Rheumatic Diseases*, the official medium of the Council, was steadily increasing, and during the past year, as a compliment to certain distinguished foreign authors, their articles had been published in the language in which they were presented as part of the Heberden Round in Paris in May, 1950. The thanks of the Council were due to the Editor of the *British Medical Journal*, Dr. H. A. Clegg, for his valuable help in all matters affecting the publication of the *Annals* which had now attained an important position among British special journals.

Dominions.—A meeting of the Dominions Committee recently formed to effect the fullest collaboration with the affiliated organizations of the Canadian Arthritis and Rheumatism Society, the Australian Rheumatism Council, and the New Zealand Rheumatism Council, was to be convened.

The three affiliated bodies had had several meetings to stimulate medical interest in the rheumatic diseases, and the Canadian Society had already established fellowships whereby young medical men could have a year's training in Great Britain or the U.S.A.

LIGUE EUROPÉENNE CONTRE LE RHUMATISME

SECOND EUROPEAN CONGRESS OF RHEUMATOLOGY, 1951

The Congress will be held in Barcelona, September 24 to 27, 1951, when the following subjects will be discussed. (The names of those taking part will be notified later.)

(1) Non-articular rheumatism.
(2) Effects of pituitary and adrenal cortex hormones in rheumatic diseases.
(3) Ultrasonic therapy.
(4) Ankylosing spondylitis.
(5) Brucellar rheumatism.

Papers will not be restricted to the above, and intending participants are asked to send their abstracts to the General Secretary as soon as possible.

It has been decided to hold an exhibition of Books and Monographs on the Rheumatic Diseases, published during the last twenty years. It would be appreciated if members could send one or more copies of each publication for this exhibition.

A tour through Spain, after the Congress, is being organized; details of arrangements will be given later.

The official Committee, to whom enquiries should be addressed, is constituted as follows:

President:	Prof. A. Pedro Pons, Mallorca 293, Barcelona.
Vice-President:	Prof. J. Gilbert Queralto, Muntaner 292, Barcelona.
General Secretary :	Dr. P. Barcelo, Casanovas 209, Barcelona.
Reports and Papers :	Dr. E. Batalla, Av. Glmo. Franco 399, Barcelona. Dr. J. Rotes Querol, Muntaner 121, Barcelona.
Organization :	Dr. R. Cirera Volta, Paseo de Gracia 86, Barcelona.
Information and Registration :	Dr. C. Alegre Marcet, Via Layetana 102, Barcelona. Dr. R. de Dalmases, Mallorca 244, Barcelona.
Housing :	Dr. J. Arcusa, Viladomat 99, Barcelona. Dr. A. Carreras, Aribau 173, Barcelona.
Post-Congress Tour :	Dr. L. Sans, C. de Ciento 301, Barcelona.

Messrs. H. Clarkson (Air and Shipping Services) Ltd., 9/10 Fenchurch Street, London, E.C.3., are prepared to arrange travel facilities.

SOCIETÀ ITALIANA DI REUMATOLOGIA

SECOND RHEUMATOLOGY DAY, ACQUI, ITALY

The second Rheumatology Day at Acqui, Italy, will take place on June 2, 1951, at the State Thermal Baths, with the support of the Società Italiana di Reumatologia. The winner of the Acqui Prize for Rheumatology will be announced. Lectures will be delivered by:

Dr. W. S. C. Copeman	President of the Ligue Européenne contre le Rhumatisme.
Prof. F. Françon	Vice-President of the Ligue Européenne.
Prof. E. Martin	Director of the University Medical Clinic, Geneva.

For information please apply to the Medical Director, Thermal Baths, Acqui, Piemonte, Italy.

ROYAL COLLEGE OF PHYSICIANS

CHRONIC RHEUMATIC DISEASES COMMITTEE

At a meeting of the Comitia of the Royal College of Physicians held on October 26, 1950, the following Committee was appointed " to consider the organization of the treatment of chronic rheumatic diseases, with special reference to the needs of the Health Service " :

Dr. W. Russell Brain (*President*).
Dr. Anthony Feiling.
Sir John Conybeare.
Dr. Frank Howitt.
Dr. W. S. C. Copeman.
Dr. W. G. Barnard.
Dr. E. T. Conybeare.
Prof. L. S. P. Davidson.
Dr. G. D. Kersley (*Secretary*).
Dr. E. G. L. Bywaters.
Sir Ernest Rock Carling.
Dr. F. S. Cooksey.
Mr. H. Osmond-Clarke.
Sir Harold Boldero.

INTERNATIONAL CONGRESS OF PHYSICAL MEDICINE, 1952

Organized by the British Board of Management of the International Federation of Physical Medicine

PRELIMINARY NOTICE

President : Lord Horder.
Vice-Presidents : Dr. Frank Howitt (Treasurer).
Dr. Philippe Bauwens (Chairman of the Executive Committee).
Dr. Frank S. Cooksey.
Honorary Secretary : Dr. A. C. Boyle.

The Congress will be held in London from July 14 to 19, 1952.

In accordance with the regulations of the International Federation of Physical Medicine, the meetings of the Congress will be reserved for matters dealing with the clinical, remedial, prophylactic, and educational aspects of Physical Medicine, and with the diagnostic and therapeutic methods employed in Physical Medicine and Rehabilitation.

In addition to the Scientific Programme, to which medical auxiliaries will be admitted as ancillary associate members, a full programme of social events and entertainment is being planned, and arrangements are being made for London and provincial visits of scientific and historical interest.

Full details will be notified later. Applications for the Preliminary Programme should be addressed to the Hon. Sec., International Congress of Physical Medicine (1952), 45 Lincoln's Inn Fields, London, W.C.2.

BOOK REVIEWS

A Text Book of Orthopaedic Medicine. Vol. II, Treatment by Manipulation and Deep Massage. By James Cyriax. 1950. Cassell, London. Pp. xv + 335, 111 plates, 10 figs. 18*s.* 6*d.*

This is a new and enlarged edition of a work formerly published under the title of *Deep Massage and Manipulation Illustrated.* As such it is well known to physiotherapists for whom it was written. The new edition should be of great value to medical men interested in " rheumatism and soft-tissue injuries ", a subject dealt with in another work by this author which is shortly to appear as Volume I of *A Text Book of Orthopaedic Medicine.* Though objecting to the title, we can wholeheartedly recommend this exposition of Dr. James Cyriax's work. It provides a manual of manipulative procedures well presented and adequately described. The methods are of special interest in that they are based upon manœuvres which do not usually require anaesthesia, the necessary relaxation being obtained by preliminary massage. Most of the work is within the scope of his well-trained physiotherapists, and he performs a notable service in spreading knowledge of such technical procedures, which should also be within the scope of medical men prepared to take a sympathetic interest in them. It is perhaps regrettable that Dr. Cyriax occasionally uses such jargon as " subluxation of the intra-articular annulus " when he means protrusion of intervertebral-disk substance and " subluxation between the capitate and lunate bones at the wrist ", which he cannot prove. We can, however, forgive such minor lapses from pathological rectitude by comparison with the excellence of method.

We return to the question of title, for it is one that recalls another. Is the subject matter of this book that of an " orthopaedic physician " ? If so, it would imply a falsification of all that we understand by the term " physician ". The study of present-day problems in all fields of medicine reveals a greater need than ever of physicians of the first rank. Dr. Kenneth Stone has already made a noteworthy attempt to outline the scope of the physician in rheumatic diseases, but he also fell into the error of regarding that as orthopaedic medicine. If such an individual as an " orthopaedic physician " exists, he must have command of the problems of tuberculosis and other infective conditions, organic nervous diseases, cardio-vascular disorders, metabolism and endocrinology, rheumatism, paediatrics, gynaecology, industrial disease, and psychiatry. In other words he must be a physician. A practitioner, however excellent, who merely treats soft-tissue injuries and rheumatism by manipulative techniques, is not a physician but a specialist in physical medicine.

NORMAN CAPENER.

Ligue Internationale contre le Rhumatisme. Yearbook, 1950. 1st edition. 7*s.* 6*d.* (U.S.A. $1.00).

Her Majesty Queen Alexandrine of Denmark, patroness of the National Danish Association against Rheumatic Diseases, having expressed the wish that the Association should present this first edition of the Yearbook to the Ligue Internationale contre le Rhumatisme, the Danish Association has considered it an honour to comply with her Majesty's wish.

The Yearbook's opening pages contain the photographs of eminent rheumatologists closely identified with the formation of the Ligue, Jan van Breemen, Fortescue Fox, and the late Ralph Pemberton. There follows a brief survey of the circumstances and meetings which, by bringing together physicians interested in the subject from all over

Europe and the U.S.A., led to the formation of an International Committee at a meeting of the International Society of Medical Hydrology in Paris in 1927. From this Committee sprang the Ligue, though interest in the subject had first been awakened at the International Congress on Physical Treatment in 1913, when Dr. van Breemen of Amsterdam initiated the idea of an institute for scientific research into the rheumatic diseases. The first world war postponed further development at that time, but the idea was revived, thanks to the energy and devotion of Dr. van Breemen, and though its progress was interrupted again by the second world war the Ligue has now grown into a world-wide movement. Of these developments the Yearbook, which is in itself a tribute to the vision and enthusiasm of the founders of the Ligue, gives an interesting historical account, with forewords by eminent physicians in English, French, and Spanish. The rules and constitutions of the Ligue Internationale, the Ligue Européenne, and the Pan-American League are set out in these three languages with lists of the officials and members of the numerous branches and affiliated societies all over the world.

Copies may be ordered through Dr. W. S. Tegner, the Secretary-treasurer, London Hospital, London, E.1. Other communications regarding this publication should be addressed to Mr. Ove de Bornemann, Støre Strandstraede 19, Copenhagen, Denmark.

CORRESPONDENCE

IRON THERAPY IN THE ANAEMIA OF RHEUMATOID ARTHRITIS

To the Editors, *Annals of the Rheumatic Diseases.* 20.2.51.

DEAR SIRS,—In your last number, the interesting paper by Dr. D. N. Ross on " Iron Therapy in the Anaemia of Rheumatoid Arthritis " states that the " results in Table II show the statistically significant superiority of the administration of iron by the intravenous route . . .". As neither standard deviations nor probabilities are furnished, the statement is untrue, and it is left in doubt whether, in fact, tests of probability have been applied or whether the term " statistically significant " is used (as so often happens nowadays) as an incantation to ward off criticism. I hope the author will be able to supply from his data this calculation, and thus complete the paper.

Yours faithfully,

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ABSTRACTS

[*This section of the* ANNALS *is published in collaboration with the two abstracting Journals,* Abstracts of World Medicine, *and* Abstracts of World Surgery, Obstetrics and Gynaecology, *published by the British Medical Association. The abstracts are divided into the following sections: acute rheumatism; chronic articular rheumatism (rheumatoid arthritis, osteo-arthritis, spondylitis, miscellaneous); sciatica; gout; non-articular rheumatism; endocrinology; general pathology; other general articles. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.*]

Acute Rheumatism

Treatment of Acute Rheumatism with Sodium Gentisate. (Prime richerche cliniche sulla terapia del reumatismo articolare acuto col gentisato sodico.) TESTONI, F., and STRANO, A. (1950). *Minerva med., Torino,* **2**, 450. 5 figs, 6 refs.

Because of the toxicity of salicylates a search is being made for compounds which have the same therapeutic actions without the side-effects. The latest to be tried is sodium gentisate, which is the sodium salt of 2 : 5-dihydroxybenzoic acid, a substance normally found in the urine of patients treated with salicylates.

Seven patients were treated with this drug in the Medical Unit of the University of Catania, and a preliminary report of their progress is presented. Five of these were young people with typical "rheumatic" histories and evidence of joint and heart involvement, the latter often of severe degree; the two other patients were older and were suffering from a generalized arthritis. The majority had already had some treatment with salicylates, with poor results. However, soon after treatment with 15 to 25 g. sodium gentisate daily by mouth in divided doses began (in the most severe cases smaller doses were given intravenously in addition), there was marked clinical improvement, even in patients with cardiac failure. More important is the fact that, even with such large doses, only one case showed signs of toxicity and these were not severe. The effect on the erythrocyte sedimentation rate was not marked, and the slow fall in this rate was unrelated to the dramatic improvement produced by the drug.

The compound has no direct antipyretic action, but is a weak analgesic and a definite diaphoretic. A comparison with salicylates shows that the latter are more active therapeutically; a point of some interest is that salicylates appear to be more effective in cases treated with gentisate. *A. Paton.*

Preliminary Report on the Use of Sodium Gentisate in Acute Rheumatism. (Prime ricerche cliniche sull' impiego del gentisato sodico nel reumatismo articolare acuto.) CAPRETTI, G., and ARDUINI, U. (1950). *G. Clin. med.*, **31**, 677. 8 refs.

Sodium gentisate was given by mouth in doses of 10 to 16 g. daily to six patients suffering from acute rheumatism. Results were disappointing, for in only two patients was there a complete remission. No evidence of gastric intolerance was seen, but drug rashes and alkaptonuria occurred. There is no point in substituting sodium gentisate for sodium salicylate in the treatment of acute rheumatism. *S. S. B. Gilder.*

Observations on the Development of Rheumatic Fever and Glomerulonephritis in Cases of Scarlet Fever Treated with Penicillin. WEINSTEIN, L., BACHRACH, L., and BOYER, N. H. (1950). *New Engl. J. Med.*, **242**, 1002. 21 refs.

A series of 167 cases of scarlet fever were treated with penicillin; the majority of patients received parenteral injections (15,000 units) every 3 hours for 10 days. Twelve patients developed what were considered to be manifestations of rheumatism, and six glomerulonephritis.

In assessing rheumatism attention was paid to such matters as latent period, fever, arthralgia, appearance of cardiac murmurs, electrocardiographic changes, and erythrocyte sedimentation rate (E.S.R.). [From the published data it is impossible to adduce how the cases were distributed in respect of these factors, so that it is difficult to sort out the material. Thus in one paragraph the average latent period is given as 9·2 days; later it is stated that "in the other twelve, joint manifestations did not appear until at least 9 days after the onset of sore throat". Yet only four of the latter cases were classified as cases of rheumatic fever.] There is a lengthy discussion of the significance of electrocardiographic changes. Most attention was paid to the P-R and Q-T interval; the former was prolonged in eleven and the latter in the same number. However, these changes were not in the same patients, nor were they necessarily noted in simultaneous records. In only one patient was the E.S.R. increased at the time when rheumatic activity was thought to be present.

All six patients with nephritis showed albuminuria casts in the urine, and haematuria after a latent period of 18 to 25 days. Three patients had fever, and in three (not necessarily the same) the E.S.R. was raised at the time of the development of urinary abnormalities. In only one patient did the authors find actual clinical evidence of nephritis.

It is concluded that the administration of penicillin in cases of scarlet fever does not prevent the development of rheumatism or nephritis; since the complication rates are similar to those encountered before the use of penicillin, it is considered that the possibility of the occurrence of these complications is not reduced by such a form of treatment.

[In the same issue there is a leading article which discusses (without adding much light) the conflicting results obtained by different investigators, particularly contrasting the above negative report with the good results obtained by Denny and others (*J. Amer. med. Ass.*, 1950, **143**, 151) in a large-scale study on Air Force personnel. The latter investigation was well controlled and deserves particular emphasis for that reason. The abstracter wonders, however, how much reliance is to be placed on the prevailing custom of diagnosing rheumatic fever on the strength of minimal changes found in serial electrocardiographic tracings. Has such a study been made upon presumably normal persons ? The abstracter suspects that such a study would show that such " abnormalities " occurred with a frequency not differing greatly from that reported in the above paper.]

T. Anderson.

Serum Mucoproteins in Children in Health and Disease with Special Reference to Rheumatic Fever. KELLEY, V. C., GOOD, R. A., and MCQUARRIE, I. (1950). *Pediatrics*, **5**, 824. 4 figs, 25 refs.

In this survey the serum mucoprotein values were calculated from the tyrosine content of the filtrate after adding perchloric acid to blood. There were 107 normal subjects and 207 patients suffering from a wide variety of diseases. In active rheumatic fever the level of mucoprotein in serum was invariably raised up to three-fold the normal, but fell to normal as activity subsided; close correlation with the erythrocyte sedimentation rate was found. The same applied to rheumatoid arthritis. When chorea was the only sign, values were normal or slightly raised, as also in cases of rheumatic fever in the inactive phase and in uncomplicated streptococcal disease of the throat. In normal children the figures were essentially the same as in healthy young adults. Marked elevation of serum mucoprotein level was encountered in some acute infections and in disseminated malignant disease. The values were consistently low in the lipoid nephrosis syndrome. *W. S. Killpack.*

Rheumatic Heart Disease in Service Pensioners. A Review of 319 Cases. HARTLEY, R. (1950). *Brit. med. J.*, **2**, 396. 6 refs.

A follow-up study was made of 318 men discharged from the Services with rheumatic heart disease. All presumably had the disease on entry. In only five was an apical systolic murmur noted on enlistment, indicating the correctness of assessment of the many men with incidental systolic murmurs accepted for service. The author is of the opinion that most of his 318 cases could have been diagnosed on entry, failure to make an adequate clinical cardiological examination being responsible for their acceptance. The incidence of aortic valve lesions in the series was very high (74 per cent.) due probably to the greater difficulty in the diagnosis of these lesions than in the diagnosis of mitral lesions. A history of previous rheumatic infection was obtained in only 37 per cent. of the cases.

Recurrence of rheumatic fever led to the diagnosis in 31 per cent. of the cases. The " expected " recurrence rate for this age-group is 5 per cent. Possibly the rigours of training increased the predisposition to recurrences, half of which occurred within 2 years of entry. Dyspnoea on effort was the presenting symptom in 27 per cent. of the cases, but in none did it appear to be precipitated by Service training. A third of the cases were symptom-free, being discovered on routine examination, although no less than 80 per cent. of the patients developed symptoms within 6 months of diagnosis due to a superimposed cardiac neurosis. Only 5 per cent. reported with haemoptysis; in many of these cases unnecessary lung investigations were carried out. Five entered sanatoria. Mass radiography accounted for the diagnosis in five cases, and bacterial endocarditis led to diagnosis in four and congestive failure in one.

Antero-posterior chest radiographs were taken of 264 of the patients after diagnosis. The heart was reported as enlarged in 81 per cent. and normal in the remainder. The high percentage of cases in which the heart was said not to be enlarged would probably have been reduced had oblique views been taken. *Ellis Dresner.*

Production of Rheumatic Subcutaneous Nodules. SCHWARTZ, S., and STEINBROCKER, O. (1950). *Amer. Heart J.*, **40**, 100. 1 fig., 6 refs.

In this paper from the Arthritis Clinic, Bellevue Hospital, New York, the literature concerning the production of " artificial " subcutaneous nodules in cases of rheumatic fever is reviewed and discussed and the authors describe their own attempts to produce nodules by three methods: (1) After infiltration of the area with procaine, 3 ml. of the patient's own blood was injected subcutaneously over the olecranon process, the patient rubbing the area for 10 minutes three times a day. (2) A 1 per cent. solution in M/400 hydrochloric acid of trypsin magnesium sulphate was passed through a Seitz filter and, within 48 hours, 1·0 ml. was injected over the olecranon. No friction was applied. (3) Fluid from the knee-joint in a case of moderately advanced (stage II) active rheumatic arthritis with naturally occurring subcutaneous nodules was tested for sterility and then (after a preliminary sensitivity test with 0·1 ml. 1 in 100 dilution) 1·0 ml. sterile joint fluid was injected subcutaneously over the olecranon. Friction was applied as in experiment (1).

Eighteen of the subjects in experiment (1), thirteen in experiment (2), and eight in experiment (3) had rheumatoid arthritis, while eight in experiment (1), six in experiment (2), and four in experiment (3) had rheumatic fever. Sixteen healthy subjects with no rheumatic history were used as controls. After 6 weeks' observation none of the subjects in experiments (2) or (3) developed nodules. In experiment (1) one of the subjects with active rheumatic carditis developed a doubtful area of induration which persisted for a fortnight, but showed a non-specific histological picture.

Peter Harvey.

Treatment of Acute Rheumatism with Rutin and Ascorbic Acid. (Tratamiento de la enfermedad reumática con rutina y acido ascórbico.) SCHNIR, M. (1950). *Sem. Méd.*, **57**, 1143. 29 refs.

The authors treated fifteen patients suffering from acute rheumatism in the Cosme Argerich Hospital, Argentina, with rutin and ascorbic acid. Patients were given 300 to 1,000 mg. rutin daily, and 500 to 1,000 mg. ascorbic acid. Total doses of rutin were 5 to 60 g., and of ascorbic acid 8 to 50 g. No untoward reactions were observed. All patients were cured, the criteria being disappearance of fever and of all articular, visceral, and cutaneous symptoms, return of the erythrocyte sedimentation rate

to normal, and disappearance of all cardiac disturbances as measured clinically, radiologically, and electrocardiographically. Fever persisted for from 1 to 8 days, and articular symptoms disappeared between the 3rd and 21st days. The heart condition became stabilized or returned to normal between the 10th and 35th days. The probable mode of action of the drugs is discussed, with special reference to changes in capillary permeability and fragility. *René Méndez.*

Relationship of Bone Marrow Plasmacytosis to the Changes in Serum Gamma Globulin in Rheumatic Fever. GOOD, R. A., and CAMPBELL, B. (1950). *Amer. J. Med.*, **9**, 330. 7 figs, bibl.

Sternal-marrow biopsy material was examined and serum γ-globulin levels (estimated by Kunkel's $ZnSO_4$ turbidimetric method) were determined in twelve normal children, 22 with rheumatic fever, fifteen convalescent from rheumatic fever, six with inactive rheumatic fever, eight with acute Sydenham's chorea, six convalescent from chorea, six with acute streptococcal pharyngitis and three convalescent from this disease. The findings show that in acute rheumatic fever plasmacytosis of the bone marrow is constant during the active phase (8 to 10 times the normal number of plasmacytes being found) and gradually diminishes with the subsidence of active signs. This plasmacytosis is significantly correlated with the plasma level of γ globulin. A similar, but slighter, change is found in patients convalescent from streptococcal pharyngitis. In chorea and inactive rheumatic fever the number of bone-marrow plasmacytes and the serum γ-globulin levels were normal. The relation between plasmacytosis and antibody production is discussed. [Elsewhere in the same issue of this journal Barr discusses the function of the plasma cell.]

Henry Cohen.

Urinary Excretion of Glucuronic and Salicylic Acids in Normal and in Rheumatic Children. TSENG, J. C. S., ELGHAMMER, H. W., and IVY, A. C. (1950). *Amer. J. Dis. Child.*, **79**, 826. 1 fig., 24 refs.

Since glucuronic acid is a component of collagenous connective tissues, it was thought likely that a disturbance of glucuronic-acid excretion might be demonstrable in rheumatic subjects, and might provide a useful aid to diagnosis in rheumatic fever. However, the output of glucuronic acid in the urine was not specifically increased in children with rheumatic fever, except when acetylsalicylic acid was given. Administration of bicarbonate with acetylsalicylic acid lowered the plasma level of salicylic acid by increasing the excretion of the latter in the urine, at the same time decreasing the excretion of glucuronic acid. No therapeutic implications could be drawn from these observations. Ascorbic acid had no significant effect on glucuronic-acid excretion, and glucuronic-acid metabolism appeared to be similar in subjects with active and inactive rheumatic fever.

M. Baber.

Changes in Skeletal Muscle in Acute Rheumatism. (Изменения скелетной мускулатуры при йстйнном ревматиэме.) GERTSENBERG, E. J., and SKOMAROVSKAJA, R. L. (1950). *Arkhiv Patol.*, **11**, No. 2, 18. 5 figs, 8 refs.

Lesions of skeletal muscle in acute rheumatism vary in accordance with the pathological changes in the heart. In cases with pure valvular defect the muscular lesions consist of swelling and atrophy of muscle fibres, loss of striation, clumping and multiplication of sarcolemmal nuclei, and occasional waxy degeneration of the fibres. The above changes are degenerative and non-specific in character. In cases with recurrent rheumatic endocarditis, there are in addition more specific features. The blood vessels are surrounded by cellular infiltrate. The muscle fibres may be fragmented and separated by serous exudate. The vascular endothelium is swollen. Fibrinoid necrosis of the vessel wall may be present. Miliary foci of muscle necrosis are also sometimes found. Granulomatous lesions consisting of lymphocytes, histiocytes, and large mononuclear cells may be found as well as patches of fibrosis. *L. Crome.*

The Effect of 3-Hydroxy-2-phenylcinchoninic Acid upon Rheumatic Fever. BLANCHARD, K. C., HARVEY, A. M., HOWARD, J. E., KATTUS, A., MARSHALL, E. K., NEWMAN, E. V., and ZUBROD, C. G. (1950). *Bull. Johns Hopk. Hosp.*, **87**, 50. 7 refs.

Because of certain of its pharmacological actions, it was thought that this drug might be effective in diseases which respond to adrenocorticotrophin. As a preliminary trial, it was employed in acute rheumatic fever, in rheumatoid arthritis, in bronchial asthma, and in disseminated lupus erythematosus.

In ten cases of rheumatic fever (with no control cases) it was given in a dose of 20 mg. per kg. on the first day, and thereafter for up to 20 days in a dosage of 10 to 20 mg. per kg. daily or on alternate days. The fever in almost all cases subsided within 2 days, but in two cases a low degree of fever persisted for some time. Joint pain and tenderness subsided almost equally rapidly, but swelling in a few cases persisted for some days. Three cases relapsed, two on the second and one on the fifth day. A second course produced a prompt response in two of these and there has been no further relapse in 3 months. The third patient became severely ill and died in spite of massive doses of aspirin. No change was observed in three other cases with myocarditis but no arthritis or fever.

Of ten cases of rheumatoid arthritis, two showed objective, and the others subjective, improvement. One of the first two relapsed after 3 months and re-treatment then failed. In none were the results as dramatic as in the cases of rheumatic fever. The dose employed was 20 to 40 mg. per kg. for about 6 days.

No effect was obtained in two cases of bronchial asthma with 20 mg. per kg. for 7 days. In a third case double this amount produced moderate subjective improvement, possibly psychogenic, with no change in the chest signs. Two patients with disseminated lupus erythematosus were given 20 mg. per kg. In one case the condition improved somewhat for 10 days, but fever and arthritis then appeared, due to drug sensitivity. In the second case, in which arthritis and pleurisy were present, there was some improvement, though the arthritis did not disappear during 7 days' treatment. The condition relapsed soon after therapy ceased.

The drug seemed non-toxic, for in eighty patients (apart from one case of drug fever) the only side-effect noticed was irritation of the gastro-intestinal tract. When the drug was taken after meals and with an equal amount of sodium bicarbonate this was no longer seen. Even with a dose of 40 mg. per kg. daily for 10 days the only ill-effect was that one patient complained of feeling light-headed. *Reginald St. A. Heathcote.*

Aetiological Factors in Rheumatic Fever. (Facteurs etiologiques de la maladie rhumatismale.) SARROUY, C., and VENEZIA, R. (1950). *Algérie méd.*, **54**, 285.

On Synergism: Penicillin and Streptomycin in the Treatment of Rheumatic Fever. (Sur le synergisme: Pénicilline-streptomycine dans le traitement de la fièvre rheumatismale.) BERGAMO, G. (1950). *Concours méd.* **72**, 2914. 9 refs.

Rheumatism in Childhood. BRAITHWAITE, J. V. (1950). *Brit. J. phys. Med.*, **13**, 197. 2 figs, 6 refs.

Sinusitis and the Prerheumatic Child. BROWN, E. E. (1950). *Arch. Pediat.*, **67**, 354. 19 refs.

Active Rheumatic Carditis in Patients Over 40 Years of Age. WROBLEWSKI, F., and MESSINGER, W. J. (1950). *Amer. Heart J.*, **40**, 345. 11 refs.

Chronic Articular Rheumatism (Rheumatoid Arthritis)

The Effect of Denervation of the Carotid Sinus in Rheumatoid Arthritis. (Action de l'énervation sinu-carotidienne sur la polyarthrite chronique progressive.) MICHOTTE, L. J., BUISSERET, J., DEVESTER, H., DONEUX, G., and HORNIATCHEVSKI, M. (1950). *Rev. Rhum.*, **17**, 141.

The authors confirm a previously reported observation that denervation of the carotid sinus is followed by stimulation of the adrenal cortex. The evidence of increased adrenocortical activity consists in: (1) the appearance of a diabetogenic effect, shown by a characteristic change in the glucose tolerance curve; (2) an increase in the serum albumin/globulin ratio; (3) a diminution of at least 50 per cent. in the number of circulating eosinophils; (4) an increase in the ratio of urinary uric acid to creatinine. These effects are observed to follow injection of cortisone or of adreno-corticotrophin.

Temporary denervation was first effected by infiltration of the region of the carotid sinus with a local analgesic. The authors then decided to study the effect on the course of rheumatoid arthritis of surgical removal of the carotid body. The operation was carried out on seven patients. One died. The other six showed the same dramatic improvement as that observed to follow administration of cortisone. Objective improvement in condition of the affected joints was obvious within 48 hours. The duration of the supposed adrenocortical stimulation is unknown, as also is the ultimate effect on the patients treated.

In a discussion of the paper, Coste remarked that tests for adrenocortical stimulation are positive not only after injection of adrenaline, but also after injection of very varied substances, and the great majority of these substances have no therapeutic effect in polyarthritis. These tests, though perhaps an index of adrenocortical activity, give no information on the production by the adrenal of substances with an anti-rheumatic action.

Kenneth Stone.

Disturbances of Sugar and Water Metabolism as an Expression of Diencephalic Disturbance in Rheumatoid Arthritis. (Störungen des Wasser- und Zuckerstoffwechsels als Ausdruck einer diencephalen Störung bei chronischer Polyarthritis.) HILLER, E. (1950). *Z. klin. Med.*, **146**, 569. 3 refs.

Studies of water and sugar metabolism in forty cases of chronic rheumatoid arthritis showed disturbances in both these functions in almost all patients, suggesting that the pituitary-diencephalic apparatus is involved in this disease. This is further confirmed by the frequent occurrence of symptoms referable to the endocrine and vegetative nervous systems, which are closely connected with the diencephalic apparatus. The author believes that these disturbances are not the cause, but a secondary effect, of the rheumatic process. They are never found in cases of acute polyarthritis. *Marianna Clark.*

Gold Therapy in Early Rheumatoid Arthritis. ADAMS, C. H., and CECIL, R. L. (1950). *Ann. intern. Med.*, **33**, 163. 12 refs.

An attempt was made to evaluate gold therapy in rheumatoid arthritis. The authors treated 106 early cases, and compared the results with those obtained in 83 controls treated by "conventional" methods. The standard of remission is not defined, but it was found that gold therapy resulted in more remissions more quickly than did the treatment given to the controls. The difference was less, however, when the two groups were assessed according to strict therapeutic criteria. No mention is made of the method of selecting cases and controls, apart from the statement that in all the cases the disease was of less than one year's duration.

D. P. Nicholson.

Pregnenolone in the Treatment of Rheumatoid Arthritis. STOCK, J. P. P., and MCCLURE, E. C. (1950). *Lancet*, **2**, 125. 8 refs.

The authors investigated the effects of △5-pregnenolone acetate in oil in one case of ankylosing spondylitis and nine cases of rheumatoid arthritis. The disease was clinically active and the erythrocyte sedimentation rate (E.S.R.) raised in all. Patients were in hospital during the trial. Progress was assessed by estimations of the E.S.R. once or twice weekly, and weekly measurements of joint ranges, grip, and joint circumferences. The drug was given intramuscularly, in daily doses of 200 mg. for 3 weeks. Control injections of oil were then given daily for two weeks and a second course of pregnenolone, combined with 1 g. ascorbic acid and 100 units hyaluronidase in the same syringe, was given for a further 2 weeks.

Of ten cases treated, three showed measurable objective improvement. One of these was the case of spondylitis, in which improvement was continued for several months afterwards. It was therefore questionable whether it could be attributed to the drug. In one of the cases of rheumatoid arthritis improvement was already occurring before treatment and the condition did not relapse when the drug was withdrawn. In only one case could improvement be ascribed to pregnenolone. In this case the condition relapsed when the drug was withdrawn or when the dose was reduced. Joint effusions and the E.S.R. remained unchanged during the remission. In most of the cases subjective improvement was noted an

hour or two after the injections, whether of pregnenolone or control oil.

Pregnenolone had no general toxic effects, but local reactions at the injection sites occurred in seven cases and were severe in five, preventing further administration in one. These local inflammatory injections (which might have been due to the solvent) were uninfluenced by the simultaneous injection of hyaluronidase. *Ellis Dresner.*

Cortisone Acetate and Terramycin in Polyarthritis of Rats. KUZELL, W. C., and MANKLE, E. A. (1950). *Proc. Soc. exp. Biol., N.Y.*, **74**, 677. 10 refs.

Arthritis induced in rats by the intraperitoneal injection of cultures of pleuropneumonia-like organisms did not respond to treatment with cortisone. Failure to respond to adrenocorticotrophin had been reported previously (Kuzell and Gardner, *Stanford med. Bull.*, 1950, **8**, 83), and the authors contrast their results with those obtained by Selye (*Brit. med. J.*, 1949, **2**, 1129) with the same hormones in formalin-induced arthritis in rats. The infection-induced arthritis responded to treatment with terramycin. *A. C. Crooke.*

The Effects of Adrenocorticotrophic Hormone (ACTH) in a Case of Juvenile Rheumatoid Arthritis. ASTRUP, P., BRØCHNER-MORTENSEN, K., FABER, V., HAMBURGER, C., HARBOE, N., SCHMITH, K., SNORRASON, E., SPRECHLER, M., and VESTERDAL, J. (1950). *Acta Paediatr., Stockh.*, **39**, 215. 8 figs, 19 refs.

The authors of this paper describe a case of rheumatoid arthritis treated with adrenocorticotrophin (ACTH). A 10-year-old girl had had rheumatic fever at the age of 1½ years. The heart was enlarged, but there was no electrocardiographic change. Following a recurrence at 2½ years she developed periodic attacks of febrile arthritis alternating with periods of comparative well-being. Three courses of gold treatment had little effect on the joints or the erythrocyte sedimentation rate (E.S.R.). The last febrile attack, in which pericarditis and anaemia developed, had started 6 weeks before the beginning of ACTH treatment, at which time she was emaciated (weight 17·8 kg., with normal height for her age), all joint movements were limited except at the toe and distal finger joints, there were contractures of the elbows, hips, and knees with atrophy of the muscles of the extremities, and she cried on the least passive movement. The lymph nodes were enlarged, but there was no splenomegaly. There was an apical systolic murmur and radiological enlargement of the heart.

At first she was given 25 mg. of ACTH daily in four intramuscular injections. Six hours after the first injection she could sit in a semi-erect position, the next day tenderness of the joints had gone, and after 3 weeks she could ride a bicycle. Her appetite improved and she gained 2·4 kg. in weight in the first week. The dosage was gradually diminished by 8 or 10 mg. a day down to 4 mg. a day without recurrence. On the 21st day a cold caused fresh arthritis of the knees and elbows which disappeared after four daily doses of 4 mg. of ACTH. From the 26th to the 50th day of treatment she was given 2 mg. a day, whereupon the temperature rose and joint symptoms recurred. One week later she started a course of 25 mg. of ACTH daily for 4 days, followed by 5 mg. daily without improvement, and treatment was stopped on the 76th day after a total dosage of 572 mg. had been given.

Proteinuria (with a maximum excretion of 9 g. daily) developed on the 16th day of treatment and, in the absence of haematuria, hypertension, or rise in blood urea level, was diagnosed as due to nephrosis. The failure of the second course of treatment at high dosage to counter the relapse was possibly associated with the fact that the ACTH was of a different batch, and the authors in an addendum report a remission of joint symptoms and a fall in the E.S.R. after the administration of 50 mg. daily of yet another batch. After 3 days this course was stopped on account of increasing oedema. A Congo-red rest showed 99 per cent. absorption of dye, indicating the presence of amyloidosis. During treatment the serum level of proteins (especially of the α-globulins), uric acid, and non-specific hyaluronidase inhibitor decreased; there was no change in the electrolyte levels in the blood, but excretion results were inconclusive. The haemoglobin level, leucocyte count, and lymphocyte count increased and the eosinophil count decreased. In the first and third periods of high dosage, excretion of both 17-ketosteroids and glucocorticoids increased, while in the second period, when there was no clinical improvement, only the former increased. *A. W. Franklin.*

Apparent Free Histidine Plasma and Urine Values in Rheumatoid Arthritis Treated with Cortisone and ACTH. STEPHENS, C. A. L., WALLRAFF, E. B., BORDEN, A. L., BRODIE, E. C., HOLBROOK, W. P., HILL, D. F., KENT, L. J., and KEMMERER, A. R. (1950). *Proc. Soc. exp. Biol., N.Y.*, **74**, 275. 2 figs, 9 refs.

A group of fifteen patients with active rheumatoid arthritis were treated with cortisone or adrenocorticotrophin (ACTH) while under controlled conditions of metabolism, their urinary excretion and plasma level of histidine being measured. In five of these patients initial doses of 300 mg. of cortisone intramuscularly were followed by 100 mg. daily; ten patients were given from 40 to 160 mg. of ACTH daily in divided doses at 6-hourly intervals. Rapid subjective and objective improvement occurred in all patients. Histidine was measured in the plasma and in 24-hour collections of urine by a microbiological technique, in which the test organism was *Leuconostoc mesenteroides P-60*. All specimens from each patient were assayed in one series and hydrous histidine hydrochloride was used as a standard. There was a striking increase in the excretion of apparent free histidine in the urine during treatment with both drugs. The plasma levels were not significantly altered, however, although the maximum values reached during treatment showed a significant rise when compared with the highest control values. *A. C. Crooke.*

Desoxycorticosterone Acetate and Ascorbic Acid Injections in Rheumatoid Arthritis. KLING, D. H. (1950). *J. Amer. med. Ass.*, **143**, 791. 8 refs.

The effect of the administration of 5 mg. of deoxycortone acetate by intramuscular injection followed by intravenous or intramuscular injection of 1,000 mg. of ascorbic acid has been studied in fourteen cases of rheumatoid arthritis; two patients received daily injections, the rest were given injections two or three times weekly. Patients were advised to reduce salt intake during treatment.

In only one patient was there objective improvement; one was subjectively improved, six were unaffected, and

six became worse, five of these last having acute exacerbations. One patient receiving daily injections developed hypertension with heart failure after the 13th injection. Another patient, who received injections every 3rd day, developed hypertension after the 6th injection. One patient given daily injections developed, after some 2 weeks' treatment, greatly increased weakness and soreness of the muscles, ascribed to a low serum-potassium level. *Kenneth Stone.*

Treatment of Rheumatoid Arthritis with Progesterone and Pregnenolone. KLING, D. H. (1950). *Ann. west. Med. Surg.*, **4**, 378. 9 refs.

The effects of progesterone therapy in forty cases of acute rheumatoid arthritis (32 female and eight male) and five cases of ankylosing spondylitis are reported. All the patients had previously had various types of treatment (including chrysotherapy in 28 cases), some with temporary benefit, but all had relapsed.

The injection of 100 mg. of progesterone daily for 7 to 30 days was followed in 20 cases by a maintenance dose of 25 to 50 mg. twice weekly. Remission or major improvement occurred in sixteen of the cases of rheumatoid arthritis, but only one of the patients with ankylosing spondylitis was benefited by the treatment. It is noted, however, that of the patients previously given chrysotherapy significant improvement had occurred at first in a similar proportion of cases. Relapse occurred shortly after cessation of treatment if no maintenance dose was given, and the maintenance dose failed to prevent deterioration in some cases, so that intermittent or continuous treatment with large doses may be necessary. There were no toxic reactions among the male patients, but menstrual disorders and post-menopausal bleeding were frequent in the females, five of whom also had mild skin reactions.

It is suggested that as progesterone and its derivatives are readily available and have few toxic effects their administration might be combined with gold therapy and could be continued for long periods.

Kathleen M. Lawther.

Studies on the Effect of Neostigmine on Muscular Symptoms in Rheumatoid Arthritis. [In English.] WRAMNER, T. (1950). *Acta med. scand.*, **138**, Suppl. 242, 1. 17 figs, bibl.

A syndrome comprising muscle pain, pain on motion, muscle tenderness to deep palpation, and decreased range of motion is common in rheumatoid arthritis. In this investigation possible causes of this syndrome and the effect of neostigmine are studied.

Thermo-electric recordings of the muscle temperature gave no support for the assumption that these symptoms are referable to any marked vasoconstriction in the muscles. The beneficial effect of neostigmine is probably not ascribable to any action on the vessels.

In electromyographic recordings from the affected muscles an involuntary activity in the voluntarily relaxed muscles was observed in 38 of 50 patients. In 36 of these 38 patients the electromyographic signs of muscle activity disappeared within 30 minutes after subcutaneous injection of 0·7 to 1·0 mg. neostigmine. Injection of normal saline showed no effect on the activity. In 34 of the 38 patients with electromyographically demonstrable muscle activity the range of motion increased significantly after the injection of neostigmine. Electromyographic recordings of the patellar reflex showed that subcutaneous injection of a small dose (0·5 to 1·0 mg.) of neostigmine decreased the patellar reflex.

The present observations favour the theory that the discussed symptoms are caused by reflex contractions in the affected muscles and that neostigmine exerts its beneficial effect by an action on the spinal reflex arc. It is possible that those authors who found no beneficial effect of neostigmine therapy administered too large doses of neostigmine.—[*Author's summary.*]

Management of Rheumatoid Arthritis with Smaller (Maintenance) Doses of Cortisone Acetate. BOLAND, E. W., and HEADLEY, N. E. (1950). *J. Amer. med. Ass.*, **144**, 365. 6 refs.

Since Hench and others first reported the beneficial effects of cortisone in rheumatoid arthritis, it has become increasingly manifest that its action is generally temporary and that relapse occurs when administration is stopped. Furthermore, adverse effects may attend its use over prolonged periods, because the hormone influences a wide variety of metabolic functions. Hence if cortisone is to become a safe therapeutic agent, methods for prolonged administration must be devised which will avoid or minimize the unfavourable reactions while preserving the effectiveness of the drug in suppressing rheumatic activity.

In this paper preliminary studies are reported which seem to show that some severe cases and most mild cases of rheumatoid arthritis may be kept under clinical control for fairly long periods with maintenance doses of cortisone, after heavy initial dosage. They have not found it necessary to give these smaller maintenance doses every day; larger doses given every other day have equally satisfactory effects. The incidence of side-effects from the hormone was decidedly less when these smaller doses were used. With average daily doses of 65 mg. or less, signs of hypercortisonism occurred in only 8·3 per cent. of patients; with the usual daily dose of 100 mg. they developed in 33 per cent. of all cases.

[This important paper should be read in full by all workers in this field of clinical medicine.]

W. S. C. Copeman.

Rheumatoid Arthritis. Effects of Certain Steroids Other than Cortisone and of Some Adrenal Cortex Extracts. POLLEY, H. F., and MASON, H. L. (1950). *J. Amer. med. Ass.*, **143**, 1474. 2 figs, 18 refs.

In an attempt to elicit specific structural requirements for antirheumatic activity, twelve steroids other than cortisone and four adrenal cortical extracts were administered to eleven patients with rheumatoid arthritis and comparison was made with the effects of cortisone and adrenocorticotrophin (ACTH) in the same subjects. Except for deoxycortone acetate, of which 5 mg. was given daily, the steroids were given intramuscularly in doses equalling or exceeding the known effective range of cortisone for 1 to 2 weeks. The adrenal cortex extracts used were Kendall's adrenal cortical extract, given in doses of 100 ml. daily intravenously, a lipo-adrenal extract and an extract in propylene glycol given intramuscularly, and an oral preparation given in capsules equivalent in glycogenic activity to 150 mg. cortisone daily. The last three preparations were given for periods of 14 to 33 days.

Significant antirheumatic activity was shown by only two of the compounds used, 17-hydroxycorticosterone (Kendall's compound F) and the adrenal cortical extract given orally in the amounts mentioned above; improvement ceased immediately the compounds were withdrawn. Euphoria, comparable to that produced by cortisone, occurred only in the case of the patient receiving the oral extract. Oedema appeared only in two cases receiving deoxycortone acetate and adrenal cortical extract, and facial rounding only in one patient treated with 50 to 100 mg. of compound F daily for 9 days. Withdrawal effects did not occur in any case. The erythrocyte sedimentation rate (E.S.R.) returned to normal in the patients receiving the oral adrenocortical extract and the extract in propylene glycol, and in one case it fell from 85 to 24 after 12 days of treatment with compound F. None of the other compounds affected the E.S.R. Increased urinary excretion of 17-ketosteroids was observed with those compounds containing a 17-hydroxyl group, with the exception of 17-hydrocorticosterone and 6-dehydrocortisone. Increased excretion of corticosteroids was produced by compound F and three other steroids with an α-ketol side-chain.

From their observations the authors conclude that "the antirheumatic properties of the steroid structure are dependent on the presence of a ketone group at carbon 3, either a ketone or a hydroxyl group at carbon 11, a ketone group at carbon 20, hydroxyl groups at carbons 17 and 21, and a double bond between carbon atoms 4 and 5". These requirements are met with only in cortisone, 17-hydroxycorticosterone, and adrenal cortical extracts containing significant amounts of these two steroids. *Ellis Dresner.*

Cardiac Disease and Rheumatoid Arthritis. BRADFIELD, J. Y., and HEJTMANCIK, M. R. (1950). *Arch. intern. Med.*, **86**, 1.

An analysis was made of the case records of 154 patients investigated in the south-west of the United States. It was decided to select 45 case records of patients aged less than 50 years and suffering from uncomplicated rheumatoid arthritis. A past history of rheumatic fever was not elicited in any of these cases. Although evidence of active disease was found in the majority of the patients, the illness was considered to be acute in only seven instances. Sixteen patients had some form of cardiac disturbance. The series included seven patients with clinical, radiological, and electrocardiographic evidence of organic heart disease but with few symptoms pointing to the presence of a cardiac abnormality. One of these patients was a woman, aged 32 years, who had suffered from rheumatoid arthritis for a period of 6 months. A soft systolic murmur was detected at the apex of the heart. A skiagram of the chest revealed slight cardiac enlargement and a prominent conus. On electrocardiographic examination the T waves were observed to be abnormal in all leads. The authors also collected data on a group of six arthritic patients with cardiac disease and a history of rheumatic fever. These patients were considered to be suffering from a disease which typified the transition from rheumatic fever to rheumatoid arthritis.

It appears that clinical evidence of organic heart disease is present in 10 per cent. of cases of rheumatoid arthritis. At necropsy on patients with this disease cardiac abnormalities are found to occur in ratios ranging from 1 : 3 to 1 : 2. The possibility exists that rheumatic fever and rheumatoid arthritis are allergic diseases with a common pathological origin. In rheumatoid arthritis, however, the cardiac lesions are likely to be less severe in character. Furthermore, the arthritic condition restricts the patient's activities. Hence heart disease is tolerated relatively well. *A. Garland.*

The Treatment of Chronic Joint Diseases with Combined Injections of Deoxycortone and Ascorbic Acid. (Die Behandlung chronischer Gelenkerkrankungen mit kombinierten Injektionen von DOCA-Ascorbinsäure.) WITZGALL, J. (1950). *Ther. d. Gegenw.*, **89**, 258. 3 refs.

Effects of Compound E in Three Cases of Rheumatoid Arthritis. (Effets du complexe adrénocortical E dans 3 cas de polyarthrite chronique évolutive.) FORESTIER, J., CERTONCINY, A., JACQUELINE, F., and GERBAY, F. (1950). *Bull. Acad. nat. Méd., Paris*, **114**, 489. 3 figs.

Rheumatoid Arthritis.
I. Clinical Effects of Testosterone and Pregnenolone Therapy.
II. Studies of Adrenocortical and Hypophyseal Function and the Effects Thereon of Testosterone and Pregnenolone Therapy. HOWARD, R. P., VENNING, E. H., and FISK, G. H. (1950). *Canad. med. Ass. J.*, **63**, 340, 342. 15 refs.

17-Ketosteroid Excretion in Rheumatoid Arthritis. FREUND, H. A., BASINSKI, D. H., and SCOTT, R. B. (1950). *J. Mich. med. Soc.*, **49**, 1076. 3 refs.

The Hemagglutination Test for Rheumatoid Arthritis. FREUND, H. A., and STULBERG, C. S. (1950). *J. Mich. med. Soc.*, **49**, 1084 and 1126. 5 refs.

Sodium Chloride Excretion in Rheumatoid Arthritis. (Beitrag zur Kochsalzausscheidung bei Polyarthritis.) FELLINGER, K., KAINDL, F., and SCHMID, J. (1950). *Med. Klinik.*, **45**, 1165.

Vitamin-D Intoxication in a Child with Rheumatoid Arthritis. HYDE, J. S., and RICHMOND, J. B. (1950). *Radiology*, **80**, 379. 3 figs, 16 refs.

The Response to Methacholine in Rheumatoid Arthritis. PERERA, G. A., and PLOTZ, C. M. (1950). *Amer. J. med. Sci.*, **220**, 307. 2 refs.

Transient Pulmonary Manifestations in Rheumatoid Arthritis. BLOOM, J., and RUBIN, J. H. (1950). *Canad. Med. Ass. J.*, **63**, 355. 3 figs, 4 refs.

The Hands in Arthritis. ENSIGN, D. C., and SIGLER, J. W. (1950). *J. Mich. med. Soc.*, **49**, 1078. 14 figs.

The Hand in Polyarthritis. (La main dans le rhumatisme chronique inflammatoire.) JOLY, L. (1950). *Rhumatologie*, **No. 3**, 103. 3 figs.

New Methods in the Treatment of Rheumatoid Arthritis. (Neue Methoden in der Behandlung der Polyarthritis rheumatica.) BOCKHORN, K. (1950). *Wien. med. Wschr.*, **100**, 604. 30 refs.

The Effect of ACTH on the Agglutination with Sensitized Red Sheep Cells in Rheumatoid Arthritis. [In English.] SVARTZ, N. (1950). *Acta med. scand.*, **138**, Suppl. 246, 240. 2 refs.

Cortisone in Rheumatoid Arthritis. Observations of Fifteen Patients. LIGHTBODY, J. J., PRICE, A. E., REVENO, W. S., and VONDERHEIDE, E. C. (1950). *J. Mich. med. Soc.*, **49**, 1085.

A Study of the Immediate Effects of ACTH on the Histopathology of Felty's Syndrome. FREUND, H. A. (1950). *J. Mich. med. Soc.*, **49**, 1065. 2 figs, 12 refs.

The Place of Splenectomy in the Treatment of Still's Disease and Felty's Syndrome. (La place de la splénectomie dans le traitement des syndromes de chauffard-Still et de Felty.) LÉGER, L., and SOURDILLE, P. (1950). *Pr. méd.*, **58**, 1013.

Observations on the Effect of Combined Injections of Desoxycorticosterone Acetate and Ascorbic Acid on Rheumatoid Arthritis. [In English.] LEWIN, E., and WASSÉN, E. (1950). *Acta med. scand.*, **138**, Suppl. 246, 99. 7 figs, 9 refs.

The Treatment of Rheumatoid Arthritis with Combined Injections of Deoxycortone Acetate and Ascorbic Acid. (Die Behandlung der Arthrosis deformans mit kombinierten Injektionen von Desocycorticosteronacetat und 1-Ascorbinsäure.) BECKER, J., and FRANKE, T. (1950). *Med. Klinik.*, **45**, 1094. 15 refs.

(Osteo-Arthritis)

Heberden's Nodes. The Nature of Osteo-arthritis of the Fingers. (Nodulos de Heberden. Naturaleza de la ósteoartritis de los dedos.) STECHER, R. M. (1950). *Rev. esp. Reum.*, **3**, 310. 5 figs, 17 refs.

[This study is from Western Reserve University, not from Spanish sources.] It is interesting to learn that Heberden's original article, published in 1802, was less than 100 words long. Heberden's nodes nearly always affect the terminal phalanges, and the terminal joint may be pathologically flexed or laterally deviated. In young people the nodes are frequently traumatic in origin and they are painful, whereas in older patients, usually women at the menopause, they are painless. The frequency of the latter type increases with age. There is a definite familial incidence, more so on the maternal side. The condition is probably recessive so far as the father is concerned. As would be expected, a high proportion of the patients have osteo-arthritic changes in other joints—changes which are not usually incapacitating but are certainly symptomatic. There is no relation between Heberden's nodes and hypertension. For these nodes to develop it is essential for the nerve supply, both sensory and motor, to be intact. For instance, it was found that in a hemiplegic patient the nodes decreased in size on the affected side.

It is quite likely that the development of the nodes and of other osteo-arthritic changes is associated with a decreased blood supply. Cases of osteoporosis in relation to vasodilatation are rarely associated with Heberden's nodes. There is sometimes a disparity between radiological and physical signs. Lateral views frequently show greater osteophytic formation than do antero-posterior ones. Sometimes the proximal phalanges show osteo-arthritic changes, and there may be cyst formation in the terminal phalanges.

Treatment is useless, primarily because of the genetic factor. The author recommends that the patient be told that the condition is a benign form of osteo-arthritis which will not precipitate invalidism and must just be endured. *Paul B. Woolley.*

Infective Osteo-arthritis of the Posterior Subtaloid Joint. (L'ostéo-arthrite sous-astragalienne postérieure.) RICHARD, A. (1950). *Rev. Orthopéd.*, **36**, 124. 2 figs.

Reviewing five cases of infective osteo-arthritis of the posterior sub-taloid joint, the author emphasizes that tuberculosis in the tendon sheaths near the os calcis is often a sign of tuberculosis in the posterior sub-taloid joint. An early radiographic sign is decalcification in the area below the joint. Three cases were treated by arthrodesis, a bone graft being passed through the neck of the astragalus down into the os calcis. *J. Agerholm.*

Treatment of Osteo-arthritis with ACTH. DALE, M. (1950). *J. Mich. med. Soc.*, **49**, 1068. 3 figs, 2 refs.

Osteo-arthritis and Body Mechanics. KRYNICKI, F. X. (1950). *J. Mich. med. Soc.*, **49**, 1070 and 1077. 3 figs.

(Spondylitis)

Brucellar Spondylitis. (Die brucellöse Spondylitis.) DI RIENZO, S. (1950). *Fortschr. Röntgenstr.*, **73**, 333. 20 figs.

The incidence of spondylitis in cases of brucellosis has been estimated at between 20 and 75 per cent. Involvement of the spine was first observed in 1897.

Any part of the spine may become the site of a lesion, but most frequently the lumbar spine is involved (80 per cent.). Sacro-iliac joints are as frequently affected as is the lumbar spine. The lesion involves bones and soft tissues (spinal cord, nerves, meninges) equally. Lesions are generally multiple, but may be single, and confined to one vertebra or one intervertebral disk alone.

Symptoms vary greatly. Lumbar pain and muscular contracture are by far the most common. The pain is resistant to all common analgesic drugs and is not characteristic. The intensity of pain, which varies from case to case, does not necessarily correspond with the extent of the pathological changes, and does not indicate the site. Variations in intensity of pain are not related to the degree of fever. If a paravertebral abscess develops subacute peritonitis may follow.

Radiological examination must be preceded by careful preparation of the patient with adequate doses of castor oil, and with one or two ampules of "pitressin" 30 minutes before the examination. In cases with peritoneal complications this is, of course, not practicable, and the accumulation of intestinal gas is neutralized by instructing the patient to breathe quietly during the exposure. A fine-focus tube or a rotating-anode tube should be employed. Lateral films, both left and right, should be taken; they provide most information. Radiological abnormalities tend to lag behind clinical symptoms and

pathological changes. In acute brucellosis the bones appear ill-defined, this appearance simulating a technical fault. In the chronic stage of the disease there is marked exaggeration of bone trabeculation, which is caused by osteoporosis. The lesion usually begins in the upper or lower vertebral epiphysis and early affects the anterior longitudinal ligament, and frequently also the nucleus pulposus. This characteristic appearance resembles Schmorl's nodes closely. Bone reaction enhances the appearance of exostoses. Erosions may appear anywhere in the vertebral body. In the later stages of the disease the intervertebral spaces begin to narrow. The vertebral bodies appear denser than usual, and bridging occurs between adjacent vertebrae. Appearances closely resemble those in Pott's disease. Radiological differential diagnosis is very difficult. The bone reaction in brucellosis is much more pronounced than that in tuberculosis, and lesions are much more destructive in the period of growth than in adult life. There are no pathognomonic radiological signs. Diagnosis is not possible on the evidence provided by a single examination; it is somewhat easier when progress is observed. The radiological pictures must fulfil the following requirements: (1) show multiple vertebral lesions; (2) show co-existing lesions in various stages; (3) show spontaneous tendency to repair.

The degree of bone destruction of the spine in brucellosis bears no relation to prognosis; large lesions may heal completely, very small ones may be associated with a grave general condition, ending in death. Large lesions of bone may cause complete incapacity of the patient. *L. G. Capra.*

The Sacro-iliac Joints in Ankylosing Spondylitis. (Les articulations sacro-iliaques dans la spondylarthrite ankylosante.) FORESTIER, J., ROTES-QUEROL, J., and JACQUELINE, F. (1950). *Rev. Rhum.*, **17**, 407. 32 figs, bibliography.

Surgical forms of Non-tuberculous Sacro-iliac Arthralgia and Arthritis. (Formes chirurgicales des arthralgies et arthrites sacro-iliaques non-tuberculeuses.) INGELRANS, P. (1950). *Rev. Rhum.*, **17**, 387. 10 figs.

Consolidation of the Pubic Symphysis in Sacro-iliac Arthritis. (Consolidation de la symphyse pubienne dans certaines arthrites sacro-iliaques.) QUEREILHAC, H. (1950). *Rev. Rhum.*, **17**, 489.

The Treatment of Ankylosing Spondylitis with Sex Hormones. (Die Behandlung der Spondylarthritis ancylopoetica mit Sexualhormonen.) MÜLLER, P., and ODERMANN, E. (1950). *Z. Rheumaforsch.*, **9**, 291. 8 refs.

Familial Occurrence of Ankylosing Spondylitis in Switzerland. (Familiäres Vorkommen von Morbus Bechterew in der Schweiz.) BÖNI, A., and HAUTMANN, F. (1950). *Z. Rheumaforsch.*, **9**, 273. 8 figs, 47 refs.

Chronic Juvenile Non-tuberculous Sacro-iliac Arthritis. (L'arthrite chronique sacro-iliaque non tuberculeuse des jeunes.) TAVERNIER, M. (1950). *Rev. Rhum.*, **17**, 482.

(Miscellaneous)

Spondylosis, Articular Fractures, and Spondylolisthesis. (Spondylolyses, fractures des articulaires, et spondylolisthésis.) MARIQUE, P. (1950). *Acta orthopaed. belg.*, **16**, 332. 16 figs.

The broad definition of spondylolisthesis is the slipping of any portion of the vertebral column upon the segment below. It is interesting to note that progressive slipping has not been observed in any of the cases here reported, nor by any other author. The condition is invariably seen in a fully developed state, though it is impossible not to envisage both a progressive sliding and an acute traumatic forward subluxation. [As a corollary, it may also be noted that manipulative reduction in the slowly progressing case has never been possible.] The role of injury to the articular processes in producing spondylolisthesis is important, and the possibility that fracture of the superior articular processes is a cause of subluxation, as well as the more common fracture of the vulnerable inferior processes, must be admitted. Radiographs taken late in many cases show the presence of an arthritis, and whether this is the cause or the result of a fracture of the articular processes is not always easy to determine.

The displacement may be small, as in the series of cases reported, and minor degrees of displacement are probably most common. The pain suffered by the patient is not necessarily proportionate to the degree of slipping. In operative treatment through a posterior approach the importance of fusing the interarticular facets of the affected vertebra is emphasized. Double lesions may be encountered. In the 6 cases reported there was a spondylosis between the third and fourth lumbar vertebrae and a spondylolisthesis between the fourth and fifth, while in another case in which fracture of the articular processes was responsible, there was a spondylolithesis between L4 and L5 and between L5 and S1. Four further non-traumatic cases and three traumatic cases of spondylolisthesis are reported.

[The terminology of the subject is becoming increasingly complicated as further studies bring new information to light. Spondyloptosis is the word used for slight degrees of slipping, and spondylochisis for the arched defect, whether traumatic or congenital. Pseudospondylolisthesis has also appeared as a term for cases of apparent slipping due to the loss of intervertebral disk space. Spondylolisthesis has also been found between L5 and S1 without any defect in the vertebral arch, due to slipping of the articular processes of the fifth lumbar vertebra over those for the sacrum. While this article helps to clarify the numerous clinical manifestations of the disease, few surgeons would now be content with the use of the contact interspinous graft, illustrated as a method of treatment.] *J. G. Bonnin.*

Physical Medicine for the Home-bound Arthritic. ERICKSON, D. J. (1950). *Brit. J. phys. Med.*, **13**, 193. 12 refs.

Comparative Tests of Parenteral Pyramidon Therapy with Special Reference to Chronic Articular Rheumatism. (Vergleichende Untersuchungen zur parenteralen Pyramidontherapie, unter besonderer Berücksichtigung des chronischen Gelenkrheumatismus.) FÄHNDRICH, W. H., and JUNKERSDORF, J. (1950). *Dtsch. med. Wschr.*, **75**, 1145. 27 refs.

Amyotrophic Lateral Sclerosis Following Polyarthritis. (Über die Amyotrophische Lateralsklerose nach Polyarthritis.) KOHLER, W. (1950). *Dtsch. med. Wschr.*, **75**, 1070. 16 refs.

Aureomycin Treatment in Confirmed Cases of Rheumatic Joint Disease. (Aureomycinbehandlung bei gewissen Fällen von rheumatischer Gelenksaffektion.) LÖVGREN, O. (1950). *Z. Rheumaforsch.*, **9**, 297.

Three Unusual Types of Sacro-iliac Joint Disease. (Trois variétés exceptionnelles d'arthrites et d'arthroses sacro-iliaques.) LASSERRE, C. (1950). *Rev. Rhum.*, **17**, 487.

Sacro-iliac Arthritis as a Cause of Isolated Lumbo-sacral Pain. (L'arthrite sacro-iliaque dans le cadre des lombosacralgies isolees.) RAVAULT, P. P., VIGNON, G., and BERTHIER, L. (1950). *Rev. Rhum.*, **17**, 483.

Sacro-iliac Tuberculous Arthritis. PARKER, D. (1950). *Med. J. Aust.*, **2**, 319. 6 figs, 6 refs.

Sciatica

Muscle Weakness and Wasting in Sciatica due to Fourth Lumbar or Lumbosacral Disc Herniations. KUGELBERG, E., and PETERSÉN, I. (1950). *J. Neurosurg.*, **7**, 270. 4 figs, 15 refs.

The authors have investigated 66 cases of muscle weakness or wasting due to fourth lumbar or lumbo-sacral intervertebral disk herniation, at the Serafimer-lasarett, Stockholm. The cases discussed are those in which the diagnosis of disk herniation was subsequently confirmed at operation. Investigation was confined entirely to a study of motor changes, and care was taken to allow for functional paresis due to pain. Clinical and electromyographic examinations were carried out on the musculature of the lower leg and foot by the current methods of investigation (Kugelberg, *J. Neurol. Neurosurg. Psychiat.*, 1947, **10**, 122). Of the 41 proven cases of fourth lumbar disk herniation, 37 showed muscular disturbance of some sort; this took the form of atrophy in 23 or a palpably soft consistency on maximal contraction of the extensor digitorum brevis in twelve; nineteen showed weakness of extensor hallucis longus, seventeen weakness of the tibialis anterior, and eight weakness of foot pronation. Of the 25 proven cases of lumbo-sacral disk herniation, there was muscular disturbances only in four—weakness and wasting of the extensor group in two and the flexor group in two. The findings indicate that the principal nerve supply of the extensor digitorum brevis is derived from the L5 segment, and the authors suggest that the constant involvement of this muscle in lesions of the fifth lumbar nerve root is due either to less segmental overlap in the innervation of the distal part of the limb than the proximal, or to the greater vulnerability of the longer nerve fibres compared with the shorter ones. The frequency of the affection of extensor digitorum brevis in fourth lumbar disk herniation is stressed.

Kenneth Tyler.

Compensation in Cases of Hernia of the Intervertebral Disk. (Considerazioni infortunistiche sull'ernia del disco intervertebrale.) BETOCCHI, G. (1950). *Rass. med. Infortun. Pat. Lav.*, **3**, 241.

Not more than 800 to 900 operations on intervertebral disks are performed annually in Italy. The author's own observations cover about forty cases, of which fifteen were operated upon.

He suggests that current views of this disorder may be unsound and that it is difficult to attribute pain, arising after chill or acute infection, to mechanical causes. Any malformation of a disk will tend to cause abnormal mechanical stress, falling particularly on adjacent structures, including nerves. By itself the degeneration and distortion of a disk may be painless. From the medico-legal aspect it is important to distinguish between symptoms caused by injury affecting the malformed parts of the spine, and symptoms which would arise from the malformation independent of injury.

The cases investigated by the author were mostly in persons engaged in physical work; he points out, however, that many persons in sedentary employment suffer from the condition, with no clear history of injury.

G. C. Pether.

Anatomical and Functional Studies on Intervertebral Disk Prolapse. (Anatomische und funktionelle Untersuchungen über den Bandscheibenprolaps.) VOSS-SCHULTE, K., and BÖRGER, G. (1950). *Arch. klin. Chir.*, **265**, 329. 15 figs, 46 refs.

The authors examined 75 post-mortem specimens of the lumbar spine in order to study the disks and the course of the spinal nerves. Definite disk changes were found in 24 cases, doubtful changes in 26, and no changes in 25 cases. [The discussion of the interpretation of the findings and their comparison with those of other authors, mainly German, is rather stamped by the long German isolation.] *J. Agerholm.*

The Indications for and Results of the Excision of Lumbar Intervertebral Disc Protrusions: A Review of 500 Cases. O'CONNELL, J. E. A. (1950). *Ann. R. Coll. Surg. Eng.*, **6**, 403. 9 refs.

Some reported results of operations for lumbar intervertebral disk protrusion are quoted and discussed.

Few of the large number of patients who have lesions of the intervertebral disks require operative treatment. If cases are carefully selected, results of operation are for the most part satisfactory in that symptoms are relieved, but evidence may remain of neurological lesions in the form of changes in sensation or power or deep reflexes. In only one case of the author's series was there an increase in weakness of the legs after operation. Ten patients were operated upon a second time because of symptoms after the first operation. In each of these symptoms were relieved by the second operation. In this series two of the 500 patients operated upon died.

For the majority of patients with lumbago and sciatica rest during the acute stage, followed later by physiotherapy, is the correct treatment. *Lambert Rogers.*

Some Aspects of the Treatment of Sciatica. [In English.] ÖSTBERG, O. (1950). *Acta med. scand.*, **138**, Suppl. 246, 289.

Gout

The Role of Glutamine in Metabolism, with Special Regard to the Formation of Uric Acid in Gout. [In English.] ÖRSTRÖM, A., and ÖRSTRÖM, M. (1950). *Acta med. scand.*, **138**, 108. 2 figs, 28 refs.

Evidence is produced to suggest that in birds, uric acid can be synthesized from ammonia salts via glutamine and hypoxanthine. In human subjects uric acid may be derived from the breakdown of substances containing nucleic acid, either in the food (exogenous) or the tissue cells (endogenous). These two sources, however, cannot account satisfactorily for the hyperuricaemia of gout. It is therefore argued that uric acid formation in gout might take place by a process similar to that described for birds. In order to prove this, the glutamine and hypoxanthine levels were estimated in the blood of various groups of patients at the Nobel Medical Institute, Stockholm. The mean glutamine level in fifteen normal subjects was found to be 9·95 mg. per 100 ml. In eight gouty patients the mean glutamine level was much lower (1·4 mg. per 100 ml.), but the hypoxanthine level was increased. In leukaemia, glutamine and hypoxanthine levels were normal. Calculations showed that the fall in glutamine level in gout could be accounted for quantitatively by the increased formation of hypoxanthine. This suggests that the glutamine had been used up in forming hypoxanthine, which would then be available to form uric acid. *G. Ansell.*

The Effect of Salicylates and Adrenocorticotrophic Hormone upon the Miscible Pool of Uric Acid in Gout. BENEDICT, J. D., FORSHAM, P. H., ROCHE, M., SOLOWAY, S., and STETTEN, DE W. (1950). *J. clin. Invest.*, **29**, 1104. 6 figs, 13 refs.

The magnitude of the " miscible pool " of uric acid in a patient suffering from severe chronic tophaceous gout has been determined by measurement of the dilution of isotope which occurred when uric acid labelled with N^{15} was injected intravenously. This pool, which increased to a value of about 31 g., or about 30 times normal, fell to a value of about 2 g., or approximately twice normal when the uricosuric doses of acetylsalicylic acid were given.

The effect of ACTH upon uric acid metabolism has been studied in both gouty and the normal male subjects. The resultant uricosuria appears to arise exclusively from an increased renal clearance of uric acid. Colchicine had no demonstrable effect upon the quantities measured.

It has proved feasible to divide miscible uric acid into three compartments: (1) in solution in plasma water; (2) in solution in non-plasma body water; (3) in the solid phase. It is predominantly the uric acid in the last of these compartments that is subject to wide excursions in response to therapy.—[*Authors' summary.*]

Effects of Adrenocorticotropic Hormone (ACTH) in Gout. GUTMAN, A. B., and Yü, T. F. (1950). *Amer. J. Med.*, **9**, 24. 1 fig., 16 refs.

A series of eleven cases of acute gout were treated with adrenocorticotrophin (ACTH). Seven, including one refractory to colchicine, responded well, though in some cases the response was not superior to that obtained with colchicine, and in four patients with an unsatisfactory response to ACTH the attack was rapidly terminated by colchicine. Cessation of ACTH therapy was followed in four cases by relapse. ACTH is not suitable for prophylactic treatment. The view is expressed that the benefits of ACTH in acute gout are unrelated to a specific uricolytic action and that the available evidence does not incriminate the pituitary-adrenal mechanism as having any specific pathogenic role in gout. *Henry Cohen.*

The Gouty Hand. (La main dans la goutte.) FRANÇON, F. (1950). *Rhumatologie*, No. 3, 91. 9 figs, 1 ref.

Adrenocorticotropic Hormone Therapy as an Adjunct to Surgery in Chronic Tophaceous Gout. DOOLAN, P. D., COBEY, M. C., and KYLE, L. H. (1950). *Sth. med. J., Bgham. Ala.*, **43**, 780. 2 figs, 7 refs.

Non-Articular Rheumatism

" Nodular Fibrositic Fever " or the Syndrome of Acute Febrile Nodular Fibrositis. (Fiebre nodular fibrositica o sindrome de fibrositis nodular aguda febril.) TARNOPOLSKY, S., and COSTA, A. (1950). *Prensa méd. Argent.*, **37**, 1640. 7 figs, 7 refs.

The authors discuss the many names describing the condition of fibrositis, and consider it to be a chronic extra-articular form of rheumatism. The picture of fever with fibrositis is very rare; one such case is described in detail, and photomicrographs are reproduced showing nodules with considerable leucocytic infiltration. The condition was characterized by fever, leucocytosis, moderate anaemia, and increase in the erythrocyte sedimentation rate. In the search for focal sepsis an apical abscess was found. The possibility of erythema nodosum was excluded.

Fibrositis secondary to arthritis, chickenpox, or other diseases is not difficult to explain, but the appearance of painful nodules in patients otherwise in perfect health is hard to account for. The appearance of such nodules, accompanied by fever and general malaise, has not been described before, although there are other recognized fibrositic conditions accompanied by fever, such as epidemic brachial neuritis and Bornholm disease.

The possible aetiology of the syndrome described is considered. It is proposed to call this condition provisionally " acute febrile nodular fibrositis " or " nodular fibrositic fever ". The characteristic findings are: (*a*) an eruption of nodules, whose fibrositic character must be confirmed histologically, and (*b*) coincident signs and symptoms of infection. After the appearance of fever the nodules persist in some places and disappear in others. Considerable relief is obtained from administration of sulphur in oil. *Réné Mendez.*

The Morbid Physiology of Muscular Rheumatism. (Zur Pathophysiologie des Muskel-Rheumatismus.) BAYER, H. (1950). *Z. Rheumaforsch.*, **9**, 210. 12 figs, 42 refs.

The author draws attention to the discrepancy in cases of muscular rheumatism between the clear-cut clinical findings of local nodular hardening and tenderness, and the absence of any pathological changes in biopsy specimens. By means of the " musculometer " he attempted to show that the nodules are the result of physiological disturbance and are due to local tetanic contractions of muscle fibres.

The apparatus is designed to lead off by skin electrodes the action currents of underlying groups of muscle fibres and, after amplification, to record the " specific tone ". The " specific tone " (Bayer and Ihlenfeldt, *Z. Kreisl-Forsch.*, 1950, **39**, 289) is proportional to the product of the average frequency and the average amplitude of the action currents of the groups of fibres recorded, the latter being itself proportional to the degree of muscle-fibre activity.

Results of this investigation in three cases are given; one was a case of lumbago, and the other two cases of spondylitis ankylopoietica, in all of which the " specific tone " was found to be raised over the palpable areas of hardening in the erector spinae muscles. Injection of 1 per cent. procaine solution reduced the " specific tone " and abolished the hardening at the site of the injection without affecting the normal increase in the " musculometer " reading on voluntary movement of the muscle.

The author concludes that the typical rheumatic nodules are the result of local tetany arising on the basis of the " idiomuscular reflex " (Hoffman, *Ergebn. Physiol.*, 1934, **36**, 15), the sensitivity of which is heightened by the disease process, possibly as a result of local vascular disturbance. Procaine injection is known to affect the proprioceptive endings in muscle while leaving the motor end-plates almost uninfluenced (Bayer, *Klin. Wschr.*, 1949, **27**, 122), thus breaking the reflex arc on the afferent side. The typical pain of muscular rheumatism is regarded as comparable with cramp and secondary to the long-sustained local tetanic contraction.

J. B. Stanton.

The Phlebological Treatment of Muscular Rheumatism. (Zur phlebologischen Behandlung der rheumatischen Arthritis.) MEYER, O. (1950). *Z. Rheumaforsch.*, **9**, 255. 2 figs, 38 refs.

Pain in the Neck and Shoulder. NEU, H. N. (1950). *Neb. St. med. J.*, **35**, 312. 3 figs.

Panniculitis. Report of Cases. JONES, P. E., LAMB, J. H., and GOLDMAN, L. (1950). *Sth. med. J., Bgham., Ala.*, **43**, 792. 7 figs, 14 refs.

Treatment of Fibrositis with Adrenaline, Ephedrine, and Belladonna Creams. HOWELL, T. H. (1950). *Lancet*, **2**, 395. 2 refs.

Endocrinology

A Preliminary Report of Twenty Patients Treated with △-5-Pregnenolone and Remissions in Rheumatoid Arthritis Following Gold Therapy. COHEN, A., GOLDMAN, J., DUBBS, A. W., and MCBRIDE, T. J. (1950). *J. Lancet*, **70**, 264. 22 refs.

The authors had available the records of a large number of patients sufferings from rheumatoid arthritis who had been treated with gold salts for a few years. Recent favourable reports of the results of treatment of such cases with cortisone, adrenocorticotrophic hormone (ACTH), and pregnenolone led them to assess their results so that the efficacy of gold and steroid therapy might be compared. The group on which they report consisted of 475 patients who had received a total of 721 courses of gold therapy and were followed-up for as long as 7 years. The dosage followed the lines usual in Britain, except that the total for the normal complete course was 1·24 g. Approximately half of the patients had remissions of from 1 to 7 years and longer. Little is known so far concerning remissions after steroid therapy, beyond the fact that they are short; continuous therapy seems, in the light of present knowledge, to be necessary, and undesirable side-effects are likely to occur as the result of prolonged therapy.

The authors have given △-5-pregnenolone during the last 6 months to twenty patients in doses of 0·3 to 12·0 g. Marked improvement occurred in twelve of these and some slight improvement in three. The authors consider nevertheless that gold salts remain the most efficacious single remedy in rheumatoid arthritis; the possibility that there may be increased benefit from a combination of gold and steroid therapy is being studied.

W. S. C. Copeman.

A Clinical and Biological Study of 29 Patients Treated with Adrenocorticotrophin. (Etude clinique et biologique de 29 malades traités par la cortico-stimuline.) COSTE, F., DELBARRE, F., BASSET, G., and LACRONIQUE, F. (1950). *Sem. Hôp. Paris*, **26**, 3047. 19 figs.

Adrenocorticotrophin (ACTH) was prepared from ox or sheep pituitary by extraction with acetone, bringing the *p*H to 11, and boiling [details of the method are given in a separate paper by Coste and Delbarre (*Sem. Hôp., Paris*, 1950, **26**, 3033)]. From 10 to 80 mg. (average 40 mg.) was given daily in divided doses for periods of 1 to 3 weeks, after a control period of observation in hospital, to 29 patients with various diseases. Inert substances were substituted at intervals. Eight patients with rheumatoid arthritis were treated; in the four male patients the response was striking, although one was already in a state of advanced cachexia and amyloidosis and died in uraemia in spite of remarkable improvement in the joint condition. Of the four female patients, two responded well, though one relapsed while still under treatment; the other two responded only partially. One case of ankylosing spondylitis responded well, but relapsed on cessation of treatment, and one case of psoriasis arthropathica improved, with some regression of the skin lesions. In six cases of rheumatic fever there was a striking response in the joint condition and a fall in temperature; pericarditis, which was present in two of these cases, was also improved, though it was doubtful whether there was any other effect on the carditis.

Marked improvement was obtained in acute attacks of gout in three cases. In one atypical case of chronic lymphatic leukaemia, which had entered into an acute phase, there was an improvement in the patient's general condition, and lymphoblasts disappeared from the peripheral blood and diminished in numbers in the marrow. A temporary response was obtained in a case of acute disseminated lupus erythematosus, with disappearance of the " butterfly " eruption and of the changes in the optic fundi, but the condition soon relapsed, the patient dying in uraemia. A slight degree of improvement was obtained in a case of dermatomyositis. In four cases of asthma the response was good, but in one of them a more severe attack followed the cessation of treatment. No response was obtained in one case of ulcerative colitis and one of pemphigus.

Side-effects from the administration of ACTH were not marked. The main effect was temporary water retention, sometimes associated with transient hypertension and tachycardia, but this subsided either spontaneously or after initiation of a salt-free diet and administration of salts such as ammonium chloride (to eliminate sodium), whether the ACTH was continued or not. Some increase in weight and rounding of the facial contour was noted in two patients, in one of whom, a man, there was increased facial hirsuties. Permanent hypertension was not induced in any case.

Robert de Mowbray.

A Comparative Study of the Metabolic Effects of Pituitary Adrenocorticotrophic Hormone (ACTH) and Cortisone. (Étude comparée des effets métaboliques de l'A.C.T.H. et de la Cortisone.) MACH, R. S., DUCOMMUN, P., FABRE, J., BORTH, R., and BARAZZONE, J. (1950). *Schweiz. med. Wschr.*, **80**, 692. 4 figs, 37 refs.

Two cases of rheumatoid arthritis were treated with 100 mg. of cortisone daily for 5 days and, after 2 weeks' interval, with 25 mg. of adrenocorticotrophin (ACTH) daily for 5 days. The pains and ankylosis improved markedly with cortisone—more so than with ACTH. Urinary output of water, sodium, and chloride was much reduced, weight increased, erythrocyte sedimentation rate and eosinophil count were both lowered, and urinary output of corticosteroids was increased during treatment with both hormones, the effect again being greater with cortisone than with ACTH. Urinary ketosteroid excretion, however, was increased only during administration of ACTH. In two other cases, one of polyarthritis and one of familial scleroderma, salt and water balance studies were made, one patient being given four times the above daily dose of ACTH, the other 2½ times the above dose of cortisone. A positive sodium-chloride and water balance was produced in each case, with an increased output of potassium in the urine and a lowering of the blood potassium level. The effect of ACTH was again to increase the output of ketosteroids [corticosteroid output not stated], whereas cortisone produced an increase in corticosteroid output and a diminution of ketosteroid excretion. *H. K. Goadby.*

Antagonism of Adrenocorticotrophic Hormone and Adrenal Cortical Extract to Desoxycorticosterone: Electrolytes and Electroshock Threshold. WOODBURY, D. M., CHENG, CHI-PING, SAYERS, G., and GOODMAN, L. S. (1950). *Amer. J. Physiol.*, **160**, 217. 3 figs, 19 refs.

Rats treated by the subcutaneous implantation of deoxycortone acetate (DCA) showed an increase in plasma sodium and a decrease in plasma potassium, chloride, and magnesium content, the plasma calcium level remaining constant. Concomitantly with these changes there was an increase in the threshold of the nervous system to the induction of convulsions by electric shock. Administration of either adrenocorticotrophic hormone (ACTH) or adrenal cortical extract (A.C.E.) to DCA-treated animals restored both the plasma sodium level and the electric-shock threshold to normal, but only partially restored the plasma chloride value and did not significantly affect the potassium level. ACTH also restored the plasma magnesium content to normal levels. The adrenals of DCA-treated rats weighed less than those of normal controls, probably owing to inhibition by the DCA of pituitary adrenocorticotrophic activity. The administration of ACTH produced adrenal hypertrophy in rats which had not received DCA, and partially restored the adrenal weight in DCA-treated rats. ACTH failed to lower the raised electric-shock threshold of rats treated with DCA after adrenalectomy.

There is thus experimental evidence to suggest that ACTH and A.C.E. may be able to correct either an excess or a deficiency of sodium in the plasma, whereas DCA acts only to increase the plasma sodium level. It is also suggested that some of the toxic effects of DCA described by Selye (*J. clin. Endocrinol.*, 1946, **6**, 117) may be due to inhibition of pituitary adrenocorticotrophic activity, thus producing a deficiency of adrenal cortical secretion. *G. Ansell.*

The Effect of Adrenocorticotrophic Hormone (ACTH) on Patients with Allergic Diseases—Facts and Speculations. SAMTER, M. (1950). *J. Allergy*, **21**, 296. 2 figs, 16 refs.

Six patients with bronchial asthma received either 0·8 mg. of adrenaline 4-hourly for 4 consecutive days or 50 mg. of adrenocorticotrophin 4-hourly for the same period. During the time of observation the excretion of 17-ketosteroids, 11-desoxycorticosteroids, and oxycorticosteroids was estimated. The results in one case are reproduced, and show a somewhat irregular parallelism between 11-oxycorticosteroid excretion and breathing reserve, both of which are sometimes high at the same period. It is also stated that attacks of bronchial asthma could be produced by prolonged administration of adrenaline. The author suggests that asthma might be produced either hormonally with participation of the cortex, the hypothalamus, the anterior pituitary gland, and the adrenal cortex, or by upset of the vagus-sympathetic equilibrium, or by local histamine release.

[The facts given are scanty and their basis is uncertain. The breathing reserve is based on a hyperventilation test which, in asthmatics, is unreliable because hyperventilation in asthmatics causes a very variable increase in bronchial spasm; the assumed normal range of excretion of 11-oxycorticosteroids is called arbitrary by the author himself, but the experimental basis of this range is not given. The speculations have little relation to the facts.]

H. Herxheimer.

Acute Disseminated Lupus Erythematosus. Report of a Case Treated with Adrenocorticotropic Hormone (ACTH), with Clinical and Metabolic Observations and Autopsy Findings. WHIPPLE, R. L., and DAVIDSON, J. K. (1950). *J. Lab. clin. Med.*, **36**, 206. 6 figs, 22 refs.

The authors report the case of a postmenopausal patient with disseminated lupus erythematosus, confirmed by biopsy, who was treated at the Emory University Hospital, Atlanta, Georgia, with adrenocorticotrophin (ACTH). The patient received 25 mg. ACTH every 6 hours for 9 days, and then every 12 hours for 2 days. There was a dramatic transient clinical and haematological improvement, but the morphological condition and ultimate course of the disease were not changed by ACTH therapy. Detailed clinical, metabolic and necropsy findings are presented [and should be consulted in the original by those interested].

N. R. W. Taylor.

Experimental Vascular Disease due to Desoxycorticosterone and Anterior Pituitary Factors. II. Comparison of Pathologic Changes. MASSON, G. M. C., HAZARD, J. B., CORCORAN, A. C., and PAGE, I. H. (1950). *Arch. Path.*, **49**, 641. 6 figs, 37 refs.

In order to compare forms of experimental hypertension produced by different means, albino rats were divided into six groups, three experimental and three control groups. The work was done at the Cleveland Clinic Foundation. In the first group, one or both kidneys were wrapped in silk, and in some cases unilateral nephrectomy was performed. Death from renal insufficiency was particularly common in animals with only one kidney (this being wrapped in silk), and hypertension soon appeared in these. The degree of atrophy did not seem to be parallel to the rise in blood pressure. The atrophic kidneys contained no abscesses, had a granular surface, and were large and greyish with an irregular surface and small white and haemorrhagic points. Lesions frequently developed in the splanchnic arteries.

In a second group, female rats after unilateral nephrectomy received 2·5 mg. deoxycortone acetate in water by subcutaneous injection daily, and 1 per cent. sodium chloride solution to drink. In the third group, unilaterally nephrectomized rats were given injections of a crude suspension of powdered anterior pituitary gland. The daily dose was either kept constant or raised; in the latter case the dose was 20 mg. for 13 days, 40 mg. for 10 days, and then 60 mg. for the rest of the experiment.

Nephrosclerosis was present in every group, the lesions and hypertension being produced most rapidly and most consistently in the second group and least regularly in the third. In the kidney the tubules were dilated and often contained erythrocytes and hyaline casts. Most of the glomeruli were large and anaemic and their capsular spaces were obliterated or contained casts. The tufts were often necrotic and hyaline. A necrotizing arteritis developed both in the kidneys and elsewhere.

The authors think that these lesions are the result and not the cause of the hypertension and that they are identical with and correspond to those in human malignant nephrosclerosis. *Peter Harvey.*

Effects of Pituitary Adrenocorticotropic Hormone (ACTH) Therapy. Electroencephalographic and Neuropsychiatric Changes in Fifteen Patients. HOEFER, P. F. A., and GLASER, G. H. (1950). *J. Amer. med. Ass.*, **143**, 620. 3 figs, 15 refs.

The neuropsychiatric effects of the administration of adrenocorticotrophin (ACTH) were studied in fifteen patients with various diseases, including rheumatoid arthritis (8), dermatomyositis (2), diffuse toxic goitre (2), schizophrenia (2), and regional ileitis (1). They received the drug 6-hourly in doses of 40 to 200 mg. a day for periods of 6 to 27 days and, in one case, of 5 months. Ten of the patients showed some degree of mental change during treatment, including euphoria in all the arthritic patients who experienced relief of pain. There was, however, also a tendency to hyperactivity, tension, and insomnia; one patient became acutely manic, while another had an episode of stupor.

The electroencephalogram was mildly abnormal in seven patients before treatment. In thirteen patients "significant changes of moderate or severe degree" appeared within 3 to 5 days of the start of treatment; they consisted in reduction of alpha-activity and the presence of waves of 3 to 7 cycles per second, random or in bursts. These effects disappeared within a week of the ending of ACTH therapy. The authors discuss various possible causal factors for the mental and electroencephalographic changes without reaching any definite conclusion. *W. A. Cobb.*

The Adrenal Cortex following ACTH: a Preliminary Report. O'DONNELL, W. M., and FAJANS, S. S. (1950). *Univ. Mich. med. Bull.*, **16**, 169. 1 fig, 8 refs.

An opportunity to study the adrenal cortex after ACTH (adrenocorticotrophin) administration arose when a woman with myeloid leukaemia and diabetes mellitus died 5 days after a 22-day course of 2,825 mg. ACTH. There were hypertrophy and hyperplasia of cortical cells with loss of lipids from the zona fasciculata but an increase in lipids in the zona glomerulosa. These changes are ascribed to the ACTH treatment.
S. S. B. Gilder.

Therapeutic Evaluation of Deoxycortone Acetate and Ascorbic Acid in Experimental Arthritis. (Vérification sur l'arthrite expérimentale de la valeur thérapeutique de l'acétate de désocycorticostérone (DCA) combiné à l'acide ascorbique.) COUTU, L. L., and SELYE, H. (1950). *Rev. canad. Biol.*, **9**, 258. 6 figs, 15 refs.

In view of the favourable results reported recently by Brownlee (*Lancet*, 1950, **1**, 157) of the use of deoxycortone acetate (DOCA) and ascorbic acid in the treatment of experimental arthritis in rats induced by means of formalin injection, the present authors have repeated his work. Their observations do not bear out Brownlee's thesis. They found no evidence of any curative value in this treatment. They point out that the conclusions Brownlee draws from his work are open to doubt on general grounds, in view of the fact that he did not use a control series of animals for his experiments.
W. S. C. Copeman.

Diabetic State with Lipaemia and Hydropic Changes in the Pancreas Produced in Rabbits by Cortisone. KOBERNICK, S. D., and MORE, R. H. (1950). *Proc. Soc. exp. Biol., N.Y.*, **74**, 602. 1 fig., 4 refs.

This work is reported from the Pathological Institute of McGill University. After a suitable period of observation two rabbits were given two intramuscular injections of 10 mg. of cortisone acetate daily, and on the third day were placed in a room where the temperature varied between −1° and −133° C., being nearer the lower limit most of the day. On the sixth day each animal received, intravenously, 10 ml. horse serum per kg. body weight. In the same room were kept pairs of control animals which received either no treatment or horse serum only. Unlimited food and water were provided. (The authors now believe that similar results would have been obtained if the animals had been kept at normal room temperature.)

Five days after the commencement of cortisone administration an increase in its lipid content caused definite cloudiness of the serum, and there was a parallel rise in the blood sugar level, with glycosuria. Although necropsy on one animal which died on the 12th day was not performed until approximately 18 hours after death, the authors feel that post-mortem change could

not have been significant in the cold room. The islets of Langerhans showed some swelling of the cells and occasional fragmentation of the cell border. In an animal killed on the 22nd day of cortisone treatment, immediate necropsy showed "hydropic-change" of the cells of the islets and ductules of the pancreas. The hydropic cells contained glycogen stainable with Best's carmine. Gomori's stain showed the vacuolation to be chiefly in the β-cells. Microscopically, these pancreatic lesions resembled those seen in naturally-occurring and experimentally-induced diabetes. The authors wonder whether the lipaemia was due to the cortisone or secondary to the disturbance of carbohydrate metabolism.

Peter Harvey.

Ephedrine in a Screening Test for Cortisone Substitutes. ABELSON, D., and MOYES, E. N. (1950). *Lancet*, **2**, 50. 1 fig., 11 refs.

Both adrenocorticotrophin and adrenaline act in the same way in normal people, producing an eosinopenia by stimulating the output of glucocorticoids from the adrenal cortex. In this paper the action of ephedrine on the adrenocortical system was tested by eosinophil counts after its administration.

The subjects of the experiment were all in-patients with pulmonary tuberculosis in a static condition, afebrile, and undergoing (or about to undergo) collapse therapy. Out of 22 subjects who received 5 minims (0·3 ml.) 1 in 1,000 adrenaline subcutaneously, the six in whom the most marked eosinopenia developed were chosen, and on another day they were given 1 gr. (65 mg.) ephedrine by mouth, the eosinophils being counted 2, 4, and 6 hours later. Thirteen subjects were given distilled water by injection as a control. In the dosage used, ephedrine caused a significant eosinopenia (from −41 per cent. to −71 per cent.) in all six subjects tested.

F. B. Cockett.

Influence of Adrenocorticotrophic Hormone (ACTH) on Differences of Potential Between Synovial Fluid and Skin in Rheumatoid Arthritis. STECK, I. E., MONTGOMERY, M. M., REED, C. I., and JOSEPH, N. R. (1950). *J. appl. Physiol.*, **3**, 84. 7 refs.

In an investigation carried out at the University of Illinois, Chicago, the potential difference between the skin and the synovial fluid of the knee-joint was determined by means of a needle electrode inserted into the cavity of the latter, and a circuit including two standard saturated potassium chloride-calomel half cells. In five males, aged between 20 and 30, with no evidence of rheumatoid arthritis, a difference of potential ranging from 0 to 5 mv. was recorded, the joint potential being positive in relation to the skin, whereas in six patients with active rheumatoid arthritis the differences ranged from 28 to 76 mv. during a control period. The joint potential in the latter, however, fell markedly during the first hour after the administration of 25 mg. adrenocorticotrophin (ACTH), and in all cases the joint potential fell to less than 5 mv. at some time during a course in which 75 mg. ACTH was given, followed by 100 mg. daily for a further 3 days. In five cases the potential difference returned to the pre-treatment level on the second or fourth day after cessation of treatment.

From these results it is concluded that "the primary effect of administration of ACTH is a metabolic process rise in the blood sugar level from 20 to 30 mg. per 100 ml. and an increase in the urinary excretion of 11-oxysteroids 17-ketosteroids and of acid. These changes are listed in detail day by day in all three cases before, during, and after treatment. A warning of the possible ill effects of cortisone is given.

G. S. Crockett.

A Study of Cortisone and other Steroids in Rheumatoid Arthritis. COPEMAN, W. S. C., SAVAGE, O., BISHOP, P. M. F., DODDS, E. C., GOTTLIEB, B., GLYN, J. H. H., HENLY, A. A., and KELLIE, A. E. (1950). *Brit. med. J.*, **2**, 849. 6 figs, 24 refs.

This study was begun with the object of testing various steroids in cases of rheumatoid arthritis; a small supply of cortisone became available, and the investigation was therefore extended.

Under controlled conditions the various substances were tested, and any showing therapeutic activity was compared as regards effect with an inert substance, namely, cholesterol. Haematological and metabolic estimations were made at the same time.

Of the steroids used—androstenedione, dehydro-*iso*-androsterone, progesterone, pregnenolone, pregnadienolone, and cortisone—only the last showed significant therapeutic activity. It was given in five cases for 10 days; in all cases the response was dramatic.

D. P. Nicholson.

Effect of Cortisone and Adrenocorticotropin Therapy on Serum Proteins in Disseminated Lupus Erythematosus. REINER, M. (1950). *Proc. Soc. exp. Biol., N.Y.*, **74**, 529. 2 figs, 5 refs.

The Effect of Combined Administration of Deoxycortone Acetate and Ascorbic acid on Pathologically Disordered Muscle Function. (Die kombinierte Desoxycorticosteronacetat-Ascorbinsäure-Anwendung in ihrer Wirkung auf die pathologisch gestörte Muskelfunktion.) TEWES, H. (1950). *Ärztl. Wschr.*, **5**, 595. 9 refs.

Stress and the General Adaptation Syndrome. SELYE, H. (1950). *Brit. med. J.*, **1**, 1383. 3 figs, 4 refs.

Note: This paper was delivered as the Heberden Oration, 1950; the above reference is to a report of the first part, and the second part was reported in full in the *Annals* (1950), **9**, 246.

Clinical Trials of ACTH. Preliminary Report. DUTHIE, J. J. R. (1950). *Edinb. med. J.*, **57**, 341. 30 figs, 5 refs.

Action of 21-Acetoxy-pregnenolone ("Artisone") Compared with that of Deoxycortone Acetate (DCA) and Kendall's Compound E (Cortisone) on Experimental Arthritis. (Action du 21-acétoxy-prégnénolone (artisone) comparée à celle de l'acétate désoxycorticostérone (DCA) et du composé E de Kendall (cortisone) sur l'arthrite expérimentale.) COUTU, L. L. (1950). *Pr. méd.*, **58**, 781. 2 figs, 5 refs.

Preliminary Report on "H 365" (*para*-Oxypropiophenone), a Synthetic Pituitary Inhibitor. (État actuel du H-365 (para-oxypropiophénone) frénateur hypophysaire de synthèse.) PERRAULT, M. (1950). *Pr. méd.*, **58**, 1010. 17 refs.

The Clinical Significance and Application of Adrenocorticotrophic Hormone (ACTH). (Bedeutung und Anwendung des adrenocorticotropen Hormons (ACTH) in der Klinik.) LOHMEYER, G., HÜSSELMANN, H., BANSI, H. W., and FRETWURST, F. (1950). *Dtsch. med. Wschr.*, **75**, 1129. 37 refs.

Studies of the Action of Cortisone (Compound E) and of Adrenocorticotrophic Hormone (ACTH). (Studien zur Wirkung des Cortisons (Compound E) und des adrenocorticotropen Hormons (ACTH).) HEILMEYER, L., FREY, J., WEISSBECKER, L., BUCHEGGER, G., KILCHLING, H., and BEGEMANN, H. (1950). *Dtsch. med. Wschr.*, **75**, 1124. 10 figs, 5 refs.

Properties and Application of Δ5-Pregnenolone with Particular Reference to its Use in the Treatment of Joint Diseases. (Proprietá ed applicazioni del Δ5-pregnenolone con particolare riguardo al suo impiego nel trattamento di certe artropatie.) WEISS, F. (1950). *Gazz. med. ital.*, **109**, 173. Bibl.

Deoxycortone Acetate and Ascorbic Acid in the Treatment of Arthritis. (Acetato di desossicorticosterone e acido ascorbico nel trattamento delle artriti.) GAMBIER, R., and RICCIARDI, L. (1950). *Gazz. med. ital.*, **109**, 182. 24 refs.

Adrenal Cortical Hormones and the Joints. (Nebennierenrindenhormone und Gelenke.) UEHLINGER, E., AKERT, K., and PIROZYNSKI, W. (1950). *Bull. schweiz. Akad. med. Wiss.*, **6**, 157. 8 figs.

The Adrenals in the Rheumatic Diseases. PARR, L. J. A. (1950). *Med. J. Aust.*, **2**, 439. 17 refs.

General Pathology

Erythrocyte Sedimentation and Plasma Viscosity Tests in Rheumatic Patients undergoing Spa Treatment. DAWSON, J. E., and SALT, H. B. (1950). *Brit. J. Phys. Med.*, **13**, 152. 8 refs.

Simultaneous estimation of the corrected erythrocyte sedimentation rate (C.S.R.) by Collins's method and the plasma viscosity (P.V.) by the method of Woodmansey and Wilson were made at weekly intervals for 3 weeks in a series of 63 patients with chronic rheumatic conditions in order to assess the sensitivity of these tests as indices of progress in patients undergoing spa treatment. Statistical analysis was made of the technical accuracy of the two methods, and only changes of more than double the widest limits of variation were regarded as significant. Detailed analyses, in five tables, are given of the results, from which it is concluded that the C.S.R. is "sufficiently sensitive to reveal slight changes in a patient's condition sometimes, but not always, associated with small degrees of clinical change". The P.V. was found to be a less sensitive test [during the relatively short period over which the patients were observed]. Note is made of the "diagnostic purposes" of these tests [although there is no elaboration of the diagnostic inferences to be deduced except in so far as they provide an indication of "abnormality"] and it is recommended that both tests be applied for such purposes. In most cases a close correlation was found between the results of the two tests. When this did not occur it was found that the C.S.R. gave a more reliable indication of the degree of activity in mild early cases of rheumatic disease, while the P.V. results were more dependable in severe cases of long duration. *Harry Coke.*

The Effect of Dicumarol on the Erythrocyte Sedimentation Rate. WIER, R. H., EAGAN, J. C., and WOLFSON, S. A. (1950). *Ann. intern. Med.*, **33**, 354. 4 figs, 11 refs.

The effect of the administration of dicoumarol on the erythrocyte sedimentation rate (E.S.R.) was studied in three patients with diseases not causing an increase in the E.S.R., and in sixteen cases of acute myocarditis. In both groups an initial dose of 300 mg. dicoumarol was given, followed by 200 mg. on the second day, subsequent doses being dependent on the blood prothrombin level, which was determined daily by Quick's method. The E.S.R. was determined (by Cutter's method) daily in the first group, twice weekly in the second.

No increase in E.S.R. was observed in the first group of patients despite a reduction in prothrombin level to as little as 17 per cent. of the normal. Nor was any correlation to be found between E.S.R. and blood prothrombin level in the patients with myocardial infarction, the E.S.R. in six cases returning to normal despite continued dicoumarol therapy, and its value in the other ten cases being unaffected by fluctuations in the blood prothrombin level. Further support is thus provided for recent assertions that, contrary to earlier reports, the administration of dicoumarol in no way diminishes the value of the E.S.R. as a gauge of progress in such conditions as myocardial infarction. *D. I. Crowther.*

A New Hyaluronidase Test Based on the Erythrocyte Sedimentation Rate. (Nowa metoda oznaczania in vitro hialuronidazy oparta na zjawisky opadania krwinek.) ZABLOCKI, B. (1950). *Polsk. Tyg. lek.*, **5**, 521. 15 refs.

The author's method for the quantitative estimation of hyaluronidase is based on the effect of hyaluronic acid in raising the erythrocyte sedimentation rate (E.S.R.). The influence of hyaluronic acid on the E.S.R. is pronounced both in normal persons and in patients suffering from various diseases in which the rate is already increased, but is reduced by previous treatment with fluids containing hyaluronidase. The minimum accelerating dose of hyaluronic acid was estimated and found to be 0·05 mg. per ml. citrated blood. For the estimation of hyaluronidase this quantity of the acid is mixed with a constant volume of various dilutions of the specimen under investigation. After 30 minutes' incubation at 37° C., 1·5 ml. citrated blood is added to each tube and the E.S.R., together with that of several control specimens (after one hour), determined. The titre of hyaluronidase in the fluid examined is calculated from the dilution at which the hyaluronic acid is deprived of its accelerating activity.

According to the author, this new method possesses the following advantages: (*a*) it is accurate and technically easy, (*b*) the time required is just over 1½ hours, and (*c*) the only materials required are 10 ml. citrated blood and a 0·25 per cent. solution of hyaluronic acid in saline.

[The original paper should be consulted for technical details.] *J. W. Czekalowski.*

Effect of 17-Hydroxy-11-Dehydrocorticosterone (Compound E) and of ACTH on Arthus Reaction and Antibody Formation in the Rabbit. GERMUTH, F. G., and OTTINGER, B. (1950). *Proc. Soc. exp. Biol., N.Y.*, **74**, 815. 5 figs, 12 refs.

The development of the Arthus reaction in rabbits given repeated intracutaneous injections of crystalline egg albumin was suppressed by the simultaneous injection of cortisone acetate or (to a less extent) of adrenocorticotrophin (ACTH). There was a close correlation between the antibody nitrogen content of the serum and the severity of the skin reaction in both treated animals and controls, indicating that cortisone and ACTH diminish the production of antibody. Moreover, when antibody was injected intracutaneously it was found that the Arthus reaction developed equally well in treated and in untreated animals. This demonstration that these hormones inhibit the development of the Arthus reaction by suppression of antibody formation is pertinent in view of the present emphasis on the general increased resistance to stress supposedly produced by treatment with these substances. *A. C. Crooke.*

Pathologic Changes Induced in Guinea-pigs by Administration of Diets Deficient in the Anti-stiffness Factor. HARRIS, P. N., and WULZEN, R. M. (1950). *Amer. J. Path.*, **26**, 595. 16 figs, 40 refs.

Guinea-pigs (but not hamsters), when fed on a diet prepared from dried skimmed milk supplemented by all the known vitamins, develop calcifying necroses in voluntary, cardiac, and plain muscle tissue, and in blood vessels, liver, and kidney. In some lesions abscesses form.

[This paper with its photographs of the remarkable arterial lesions should be inspected by all interested in vascular disease.] *D. M. Pryce.*

Other General Articles

Rheumatism-like Granulomata in the Myocardium of Tuberculous Patients. (О ревматоидных гранулемах в миокарде т уберкулезных больных.) GRITSMAN, N. N. (1950). *Arkhiv Patol.*, **11, No. 2**, 65. 4 figs, 28 refs.

In a necropsy series of 81 cases, granulomatous lesions resembling rheumatic nodules were found in 23 bodies of patients dying from various forms of tuberculosis, coexistent rheumatism having been as far as possible excluded by reference to clinical history. Such lesions were not, however, identical with true Aschoff nodules. The author regards them as a manifestation of an allergic reaction, and does not agree with those Japanese workers who considered them evidence of the tuberculous aetiology of rheumatism. *L. Crome.*

Rheumatic Lesions of the Lungs and the Skin. (Ревматическое поражение легких и кожи) BEGLARJAN, A. G. (1950). *Arkhiv Patol.*, **11, No. 2**, 85. 3 figs, 10 refs.

A case of rheumatic heart disease is recorded with lesions in the lungs and a rheumatic purpura of the skin. Histological study of these lesions revealed fibrinoid necrosis of blood vessels with a polymorphonuclear infiltration of all vascular coats. The alveoli of the lungs contained fibrinous masses. *L. Crome.*

Cases of Chronic Internal Derangement of the Temporomandibular Joint Treated by Manipulation. HYNES, W. (1950). *Brit. J. plast. Surg.*, **3**, 141.

The term "internal derangement of the temporomandibular joint" covers a wide range of conditions, and the description of any sub-grouping is welcome. The author separates out a group of cases in which symptoms are due to chronic capsular shortening, usually situated in the external lateral ligament; shortening may be due to rupture of the fibres by violent stretching of the joint, or may in some cases be associated with a close bite. Sometimes the capsular shortening may be generalized, as after prolonged fixation. The leading symptom is pain when the shortened capsule is stretched; there is no pain while the jaw is at rest. Clicking may be present, but no true locking. Pain appears when the jaw is opened more than a centimetre or so. Lateral movement towards the sound side is painful if the external lateral ligament is shortened. The treatment consists of stretching the shortened ligament under anaesthesia.
C. L. Heanley.

Larsen-Johansson Disease of the Patella. Seven New Case Records. Its Relationship to other Forms of Osteochondritis. Use of Male Sex Hormones as a New Form of Treatment. WOLF, J. (1950). *Brit. J. Radiol.*, **23**, 335. 7 figs, bibliography.

The author reviews the literature on Larsen-Johansson disease, an osteochondritis involving an accessory centre of ossification at the inferior margin of the patella.

Seven new cases are presented, one of which was associated with Osgood-Schlatter disease of the contralateral tibial tubercle. In the other six cases there were no symptoms, the patients being young people with a history of recent trauma to the knee or the condition being discovered in a routine search among one hundred sets of knee radiographs. The latter search suggested a possible incidence of 2 to 5 per cent.

The use of male sex hormone in therapy is discussed and its effect described in one case, in which improvement in the condition of the tibial tubercle as well as that of the patella appears to have resulted. The author considers that male sex hormone therapy is an important adjunct in the treatment of these osteochondritides.
A. M. Rackow.

Arthro-onychodysplasia. Hereditary Syndrome Involving Deformity of Head of Radius, Absence of Patellas, Posterior Iliac-Spurs, Dystrophy of Finger Nails. BRIXEY, A. M., and BURKE, R. M. (1950). *Amer. J. Med.*, **8**, 738. 9 figs, 27 refs.

A hereditary syndrome consisting of: (1) deformity and luxation of the head of the radius; (2) hypoplasia or complete absence of the patellae; (3) posterior iliac spurs; and (4) dystrophy of the finger nails is reported, of which two cases were examined at the Department of Medicine of the University of Oklahoma. The first patient, a 26-year-old man, was admitted to the University Hospitals in terminal uraemia due to chronic nephritis. A bilateral webbing between the arm and forearm was noticed and led to the detection of the other congenital deformities. This patient's mother was subsequently examined and showed similar anomalies. Her only symptoms were inability to extend the forearms, limitation of pronation and supination, and some difficulty in

walking. In this family of sixteen members in five generations six have been affected with the syndrome.

The literature is reviewed and the hereditary aspects of the syndrome discussed. The authors believe that these structural anomalies are probably brought about by the action of a mutated gene in early embryonic development.

R. N. Johnston.

Bony Tumours in Paget's Disease. (Les tumeurs osseuses de Paget.) CORNIL, L., PAOLI, J., GASTAUT, H., and SPITALIER, H. (1950). *Sem. Hôp. Paris*, **26**, 2347. 7 figs, bibl.

Four cases of Paget's disease, with a total of ten tumours, are reported. Among these, three types of benign tumour were noted [an observation stated by the authors to be original]. These types are named: (*a*) simple fibroma; (*b*) simple or metaplastic histiocytoma; (*c*) hypertrophic giant-cell histiocytoma. The malignant tumours described are: (*a*) polymorphic reticulosarcoma; (*b*) reticulosarcoma with myeloplasia. In none of the cases were visceral metastases present, but all ended fatally.

The conclusion drawn is that the tumours arising in this condition are poorly differentiated connective-tissue tumours, and may be benign or malignant. They may arise in local or generalized forms of the disease, and may be the first feature to draw attention to the underlying disease. [Good photomicrographs are presented. The radiographic diagnosis is only briefly discussed.]

Donald McDonald.

James Currie and Hydrotherapy. COSBY, C. B. (1950). *J. Hist. Med.*, **5**, 280. 1 fig., 10 refs.

Vertebral Manipulation in the Treatment of Lumbago, Sciatica, and Cervico-brachial Neuralgia. (Les manipulations vertébrales dans le traitement des lombalgies des sciatiques et des névralgies cervico-brachiales.) RAVAULT, P., and VIGNON, G. (1950). *Lyon méd.*, **183**, 193.

Rheumatic Nephritis. ROBERTSON, H. F., and SCHLAMOWITZ, S. T. (1950). *Ann. intern. Med.*, **33**, 708. 1 fig., 12 refs.

"Steramin" in the Treatment of Rheumatic Disorders. (Steramin in der Behandlung der rheumatischen Erkrankungen.) KRAMMER, F. (1950). *Wien. med. Wschr.*, **100**, 544. 3 refs.

Procaine in Rheumatic Diseases. LIPKIN, E. (1950). *J. Mich. med. Soc.*, **49**, 1081.

A Possible Relation between Irradiated *Para*-amino-benzoic Acid and Rheumatic Fever. Part I. BASSIOUNY, M. (1950). *J. roy. Egypt. med. Ass.*, 33, 615.

A Preliminary Report on the Effect of Irradiated *Para*-amino-benzoic Acid in Rheumatic Conditions. Part II. EL-MOFTY, A., and BASSIOUNY, M. (1950). *J. roy. Egypt. med. Ass.*, **33**, 617. 1 fig., 4 refs.

The Significance of Tuberculous Infection in Rheumatism. (Die Bedeutung der spezifischen tuberkulösen Infektion beim Rheumatismus.) MLCZOCH, F. (1950). *Wien. klin. Wschr.*, **62**, 554. 21 refs.

The Psychic Components of Pain in the Rheumatic Diseases. (Les composantes psychiques de la douleur dans les affections rheumatismales.) DUVAL, A. R., and WIBROTTE, J. (1950). *Concours méd.*, **72**, 2415.